NIH AIDS Research Program Evaluation

CLINICAL TRIALS AREA REVIEW PANEL

Findings and Recommendations

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Table of Contents

Appendixes

Executive Summary

A. Introduction

The Clinical Trials Area Review Panel was charged with assessing the current National Institutes of Health (NIH) portfolio in clinical trials, developing the goals and priorities for the next phase of NIH AIDS clinical trials research, and making recommendations to ensure that these goals and priorities will be met. Specifically, in defining a vision for the future of NIH clinical trials research, the Panel addressed the effectiveness, optimal focus, balance, duplication, and cooperation among funding Institutes, Centers, and Divisions (ICDs), and the role of the Government vis-a-vis the private sector.

NIH clinical trials of therapeutics for human immunodeficiency virus (HIV) infection and its sequelae have led to improved survival and quality of life. Despite solid contributions to the standard of care, there are inconsistencies about the direction, structure, and leadership of the existing clinical trials efforts.

B. Evaluation

1. A number of ICDs have implemented clinical trials programs. Some of these programs are successfully interdigitated and collaborate productively, while others appear to function independently with little interest in collaboration. This is critical because HIV/AIDS is a multisystem disease requiring diverse clinical research expertise and because limiting unnecessary duplication of effort will permit the best return for the intrinsically high cost of clinical trials. The Panel was distressed by the absence of any overall NIH coordination of its clinical trials programs.

2. The majority of the clinical trials efforts are sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). The Panel was impressed with the contributions of the adult and pediatric AIDS Clinical Trials Groups (ACTG) in improving therapy for HIV/AIDS and its associated complications but identified drawbacks in these networks. While the scientific impact of the newer Community Programs for Clinical Research on AIDS (CPCRA) on patient management is much less apparent, it has accomplished the goal of establishing research capability in community-based clinical trials, has made an important contribution to database structure and data management, and has the potential of making a meaningful contribution to the Phase III/IV research effort. The Mycoses Study Group (MSG), working in collaboration with the adult ACTG, has been productive in establishing the standard of care for systemic fungal disease in AIDS patients. The Division of AIDS Treatment Research Initiative (DATRI) has made the smallest contribution to therapeutics research. The Strategic Program for Innovative Research on AIDS Treatment (SPIRAT) is too new to permit adequate assessment at this time. The existence of multiple clinical trials systems has resulted in difficulty in coordination of scientific agendas, loss of efficiency, and perceived overlap in mission.

3. The level of sophistication of the NIAID-funded investigators, especially those of the ACTG, is impressive. Over the past 10 years, this knowledge expansion has resulted in a mature cadre of investigators who are now capable of leading the clinical trials effort without excessive involvement by NIAID program staff.

4. Each study within the adult and pediatric ACTGs has a uniquely structured database. This system is cumbersome and makes both single-study and cross-study analyses costly and time-consuming. Potential exploration of this 47,108 (cumulative) patient database for cross-study analyses is severely impeded, as are longitudinal analyses of patients who have entered a number of studies sequentially or who are simultaneously co-enrolled in more than one study. The database for DATRI is almost nonexistent. The creation of a standardized patient-based database that facilitates such analyses is an important contribution of the CPCRA. Each of the non-NIAID trials programs also has its own statistical center, with no compatibility between databases. The Panel believes that this is a problem that should be rectified.

5. The Panel recognized the contributions of ICDs other than NIAID in the clinical trials arena. The effectiveness and willingness of some ICDs and the NIH Clinical Center to assume responsibility for scientific guidance and fiscal support of clinical trials in subject areas unique to their mission ranged from excellent to poor. The model relationship is that which has developed between NIAID and the National Institute of Child Health and Human Development (NICHD) for pediatric clinical trials. While the early relationship between the two Institutes and their respective investigators was not smooth, it has evolved over the past 10 years. It now thrives on the unique scientific contributions of NICHD- and NIAID-supported investigators and program staff, and on the complementary research capabilities supported by the different funding mechanisms including contract and cooperative agreement, respectively, utilized by each ICD.

   Other ICD clinical trials efforts include:

   a. The collaboration between the National Eye Institute (NEI) and NIAID through the interaction of the Studies of the Ocular Complications of AIDS (SOCA) and the adult ACTG has advanced both the management of cytomegalovirus (CMV) retinitis and the manner in which it is studied. ACTG support is utilized in varying ways at 9 of the 11 original SOCA sites where there is an associated AIDS Clinical Trials Unit (ACTU). However, ACTG infectious disease-trained investigators have not been fully included in the design of SOCA studies. As a result, these trials have failed to adequately explore the impact that better control of CMV replication may have on HIV disease progression and the impact of antiretroviral therapy on CMV reactivation. Competition between the SOCA and ACTG has resulted in unnecessary duplication of effort.

   b. The National Institute of Neurological Disorders and Stroke (NINDS) has not demonstrated a commitment to the clinical evaluation of therapies for the specific neurologic manifestations of HIV disease, and has not supported neurologic evaluation of HIV disease progression or of drug toxicity in trial participants. NINDS provided

minimal and limited support of neurologists working within the ACTG through a program project grant awarded in FY 1993 to the then-chair of the ACTG Neurology Committee. The limited (2-year) duration of this support is inadequate and too restricted to permit a fair evaluation of either the investigators' progress in pursuing their research agenda or the utility of this funding mechanism intended to supplement the major adult trials network. The role of NINDS in the conduct of clinical trials has been inadequate and should be addressed.

c. A commitment by the National Cancer Institute (NCI) to an appropriate level of funding for extramural clinical trials research on AIDS-related malignancies remains unclear. The newest program, the AIDS Malignancy Consortium (AMC), is a very small-scale Phase I/IIA effort. The Cooperative Oncology Groups (COGs) represent NCI's established mechanism for the conduct of Phase III trials; it has been proposed that COGs would conduct Phase III trials on AIDS-associated malignancies as well. However, there are problems with this approach. Potential participants receive their primary HIV care from AIDS specialists and infectious diseases-trained physicians; they may also be enrolled in antiretroviral and opportunistic infections (OIs) trials when a malignancy is diagnosed. Entry into a COG trial would require co-management by HIV- and oncology-based physicians and co-enrollment in two different trials networks. Similar to the SOCA effort, the COGs themselves lack the expertise in infectious diseases to design and conduct trials for AIDS-associated malignancies that include an appropriate focus on the infectious aspects of HIV disease. Optimal trial design and patient management strategies require active collaboration with infectious disease investigators. Thus, additional mechanisms for these studies should be identified.

d. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has supported investigator-initiated grants for small, intensive basic and applied clinical research studies in metabolic and endocrine disorders, including wasting, with the assumption that useful therapeutic approaches and paradigms for patient assessment will be utilized by the adult ACTG for the conduct of larger comparative trials. This assumption has not yet been fully tested but offers a potential model for inter-Institute collaboration. The recent active participation of some NIDDK-supported investigators in the ACTG program for wasting syndrome is a promising first step. This collaboration should be supported and fostered.

e. The National Institute of Mental Health (NIMH) has expended considerable resources to conduct a single comparative clinical trial of peptide T for HIV-associated neurocognitive abnormalities. The creation of a resource-intensive network to study an isolated aspect of HIV disease is not an effective use of NIH support.

f. Components of the various intramural programs conducted at the NIH Warren Grant Magnuson Clinical Center appear to compete unnecessarily with the extramural trials efforts in some cases. There is a need for better coordination and cooperation between intramural and extramural efforts to limit this duplication of effort.

6. The Panel recognizes the need for close interaction between NIH clinical trials and pharmaceutical industry-sponsored studies. Historically, some NIH Phase III trials duplicated licensure trials performed by industry or studies were initiated which might best have been performed by industry.

7. Review of clinical trials programs has been uneven. *Ad hoc* groups assembled to review the responses to targeted initiatives often do not possess the requisite expertise in HIV clinical trials to provide the insightful evaluation required of study sections.

8. A better definition of AIDS and AIDS-related research is needed. Some ICDs, particularly NCI, the National Institute on Drug Abuse (NIDA), and NIMH, appear to have coded funded research project grants as "AIDS" or "AIDS-related" although the connection to AIDS research was tenuous or nonexistent. For example, a series of program project grants in diagnostic radiology and imaging techniques funded by NCI were coded as AIDS research. Only a few subprojects relating to diagnosis of central nervous system mass lesions and accounting for a very small percent of the total funding could be seen as being potentially AIDS-related. On the other hand, funds coded by NIAID appeared almost uniformly to accurately reflect AIDS research. In fact, areas that could legitimately be classified as AIDS-related, such as basic, applied, and clinical research on opportunistic pathogens, are supported by NIAID with non-AIDS monies. As a result, the AIDS OI effort cannot be accurately tracked by the fiscal oversight systems currently in place. Within the NIAID AIDS budget, formulas appear to have been constructed that artificially distribute AIDS funds across a broad range of research areas. For example, fixed percentages of the support for NIAID extramural trials networks are arbitrarily coded as supporting research areas outside of therapeutics research, such as etiology/pathogenesis and epidemiology/natural history. These fixed, arbitrary assignments appear to have been made irrespective of any correlation to what is actually being done in these areas as part of the clinical trials effort.

I. Recommendations

1. Create a clinical trials coordinating group with broad scientific and community representation, including representatives of ICDs that conduct clinical trials, to coordinate and facilitate inter-Institute collaboration.

This advisory body would be the responsibility of the Office of AIDS Research (OAR) Coordinating Chair for Therapeutics and would report to the Director of the OAR. Other critical functions would include the responsibility to define an overall mission statement for NIH-sponsored therapeutics research, to eliminate redundancy among the various NIH trials programs, and to continually evaluate the appropriate magnitude of the entire clinical trials effort. The focus of this group would be on strategic decisions rather than on operational details or a protocol-by-protocol review. For example, this group would be responsible for deciding which patient population(s) and/or network(s) is best-suited to pursue a scientific goal of broad interest, such as the question of whether early antiretroviral therapy can alter the subsequent course of the disease. The group would help to determine the boundary between useful replication of important trial results and

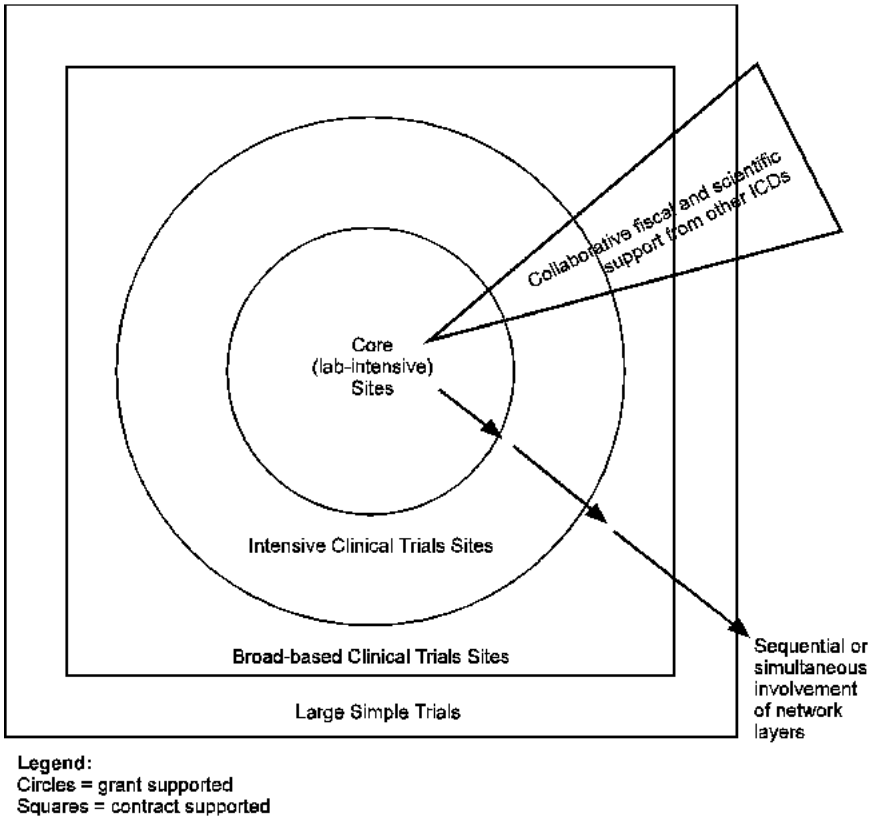
unnecessary duplication of effort and ensure appropriate collaboration among programs and their sponsoring ICDs.

2. Create a single adult clinical trials network to replace the separate ACTG, CPCRA, DATRI (and possibly SPIRAT) programs under the auspices of the NIAID.

This trials network is envisioned as one that would exhibit extraordinary flexibility, sound scientific leadership, and a range of clinical research capabilities to meet the future challenges of therapeutics research. The use of more than one funding mechanism for support of different elements of the network should provide maximum flexibility.

The proposed network would consist of several levels of clinical trials capability. Essential core elements would be funded by the cooperative agreement (grant) mechanism, including: a limited number of research sites with expertise in innovative clinical trials design; the intensive clinical and laboratory monitoring required by pilot studies; data management and statistical analysis; an operations center; central group administrative support; laboratories capable of sophisticated assays in the areas of virology, immunology, pharmacology, and opportunistic pathogens; a central specimen repository; and discretionary funds to provide additional flexibility to meet emerging needs (see Figure 1).

Figure 1. NIAID Proposed Integrated Adult Clinical Trials Network



Legend to Figure 1.

Core sites: capacity to design and perform initial pharmacokinetics and proof-of-concept studies requiring intensive virologic, microbiologic, immunologic, and pharmacokinetic and pharmacodynamic support; discretionary funds to meet emerging needs should be available (typical emphasis: Phase I/IIA trials).

Intensive clinical trials sites: capacity to design and perform intensive studies requiring close clinical and safety monitoring and the ability to obtain/process/store/ship appropriate specimens for virologic, microbiologic, immunologic, and pharmacokinetic and pharmacodynamic evaluation (typical emphasis: Phase IIB/III trials).

Broad-based clinical sites:* capacity to design and perform clinical studies that do not require intensive clinical trial site monitoring, specimen collection (other than routine labs), or data collection. These trials may include NDA-enhancing and optimal management strategy trials, (typical emphasis: Phase IV and some Phase III trials).

Large simple trials:* individual practitioners with the capability to perform Phase IV, post-licensure studies with minimal data collection (typical emphasis: Phase IV standard-of-care/optimal strategy trials).

Central support for network ([central support elements not shown in figure] grant-supported):

- Data management and statistical analysis
- Group administration, including operations office
- Specimen repository
- Sophisticated laboratory capabilities (virologic, immunologic, pharmacologic, microbiologic)
- Discretionary funds to meet rapidly emerging needs

* Contract mechanism should permit expansion and contraction of these components as dictated by scientific need.

Reference: I. Executive Summary; Recommendations
II. Evaluation A. Adults Trials, 1. NIAID, Needs

In addition to classical pharmacokinetics trials, core sites should be capable of designing and performing intensive pilot studies that evaluate microbiologic and immunologic dynamics in response to therapeutic interventions. A larger number of sites, also supported by a cooperative agreement, would be capable of performing complex trials that require intensive endpoint evaluation and close monitoring for toxicity. These sites would have the ability to appropriately obtain, process, store, and ship specimens for virologic, microbiologic, and immunologic testing. This combination of research sites would provide the appropriate capability for advancing early exploratory work to Phase IIB and III studies. A flexible number of research sites, supported by contract, would provide access to sufficient numbers of patients with diverse demographic characteristics for Phase IV and some Phase III trials. These large studies of fairly well-characterized agents would require less intensive clinical and toxicity monitoring. A master contract mechanism, similar to the one used for NICHD-supported sites in the pediatric ACTG, may permit the rapid expansion and contraction of the accessible patient base as scientific needs dictate. Additionally, individual clinical investigators who meet specific criteria should have access to trials on a protocol-by-protocol basis as Phase IV investigators. Participation of these investigators in large, relatively simple studies requiring very limited data collection may be adequately supported by modest funding on a contractual basis. It is also possible that access to new agents and multidrug combinations through these trials may provide sufficient incentive to physician investigators and their patients, precluding the necessity for direct support, particularly if data requirements are minimal.

This model, employing a mix of support mechanisms, borrows from the existing pediatric ACTG structure, where it has provided both scientific leadership and access to adequate numbers of trial participants. The different levels of research capability within the network could be used sequentially, moving in stepwise fashion from Phase I/IIA studies performed by core sites to large Phase III/IV investigations performed by the entire network. These elements could also operate contemporaneously: core sites could enroll

patients and perform sophisticated microbiologic and immunologic assays for a defined subset of the patients accrued networkwide into large randomized trials. The network should strive to perform only those studies of the highest scientific quality and avoid conducting studies that are redundant with pharmaceutical industry efforts. Studies that define optimal treatment strategies are consistent with this mission.

Leadership for the proposed network should emanate from the investigators. NIH program staff should be involved in the scientific priority-setting process; however, input should be timely, and once decisions have been made to proceed with a given study, ICD program staff should provide necessary logistical support to ensure its success. It is important that trials be implemented efficiently and expeditiously and that innovative ideas for pilot and proof-of-concept studies be encouraged. The network should be structured so that it is capable of swift review of new proposals. While such review must be scientifically and logistically sound, it should guard against the inherent tendency of large organizations to be too conservative. There should be mechanisms for encouraging innovative ideas from both young and established investigators and for vesting new investigators in the group. This will not only foster the mentoring of new investigators with novel ideas but will also prevent stagnation and a "closed shop" mentality. The network should be open to ideas for new trials and to research proposals that will use the specimen repository. The existence of banked specimens that are correlated with extensive clinical data would be a unique resource for the entire AIDS research community, and should be made available to qualified investigators. A formal procedure for submitting and reviewing proposed research requiring access to these specimens should be established.

The Panel believes that the proposed network would provide a coordinated, flexible clinical trials mechanism that would serve as the core trials resource for the optimal assessment of novel approaches to therapy, not only for NIAID but for all Institutes involved in therapeutics research. The implementation of the network should be the responsibility of NIAID staff, and the basic infrastructure support should come from NIAID. However, additional funding and scientific support should be provided by all ICDs that use it, as described below.

In the interim, the Panel supports the current initiatives to allow the scientists of the three large trials networks (the adult and pediatric ACTGs and the CPCRA) to establish their own scientific agenda. There should be adequate time to evaluate the impact of recent organizational changes in the ACTG and CPCRA, as the evolution of these programs will provide valuable experience in designing the proposed integrated network.

3. A standard for databases for all NIH-funded HIV/AIDS clinical trials should be developed that would allow for cross-study analyses and longitudinal followup of participants.

This recommendation does not mean that there should be a single statistical center for NIH clinical trials, but rather that databases should be constructed to allow greater ease of sharing and combining data. These standards must address compatibility of database software, common names for variables, common definitions, and common conventions for

followup, so that data can be shared among studies within a given program and across programs. These standards should apply at least to a minimal data set of key baseline, outcome, compliance, and toxicity data. This seamless database would allow for collection of data from the time subjects first enter a trial until their demise. In order to facilitate collaboration and cooperation among AIDS clinical trials networks, all future trials should be subject to such standards.

For the current ACTG, the development of a patient-based database that meets the above standards would simplify and expedite the primary analysis for each study as well as improve the capability to do cross-study analyses and long-term followup. While costly, restructuring the adult and pediatric ACTG database should be implemented before the next funding cycle begins (2000). At a minimum, existing or completed trials should have their databases abstracted to the minimal data set and converted to the new standards when they are available.

HIV/AIDS clinical trials methodological research has been limited. The Panel recommends the investment of research resources in the funding of innovative approaches to methodological and biostatistical issues. As an added benefit, such research should generate findings that are applicable to all clinical trials.

4. In general, all ICDs involved in HIV/AIDS clinical trials research should fully utilize and support the single NIAID-sponsored trials network described above. Each relevant ICD should contribute both scientific guidance within its area of expertise and funding support for the conduct of Phase II-IV trials rather than create anew the capacity to conduct such studies independently.

While ICDs that concentrate on organ-specific manifestations of HIV disease, such as NEI, provide tremendous expertise, the design and implementation of clinical trials should include investigators knowledgeable about the multisystem nature of HIV disease and its complications. Moreover, such collaborative efforts can be expected to result in a cost-effective use of NIH-supported resources.

The Panel offers the following specific recommendations:

4a. Future SOCA/ACTG collaborative studies should be developed that consider the other systemic manifestations of CMV disease, the potential interactions between CMV and HIV and their effect on both CMV and HIV disease progression, the antiretroviral effects of some CMV therapies, and the effect of anti-CMV therapy on CMV viral load and the development of resistance. This requires NEI support for a fully collegial interaction between the ophthalmology and infectious disease investigators.

4b. The role of and level of support from NINDS for clinical trials of therapy for the neurologic manifestations of HIV/AIDS, as well as for evaluation of possible neurotoxicity, has been inadequate. The commitment of NINDS to such clinical trials should be addressed by the Institute Director.

4c. NCI support of extramural trials has been limited to date. The recent initiative that created the AIDS Malignancy Consortium (AMC) in 1995 for the exploration of innovative Phase I/II pilot studies is underfunded. Although additional support for HIV virologic and immunologic testing has been promised by NCI, it remains to be seen whether this is a viable Phase I/IIA research program at the current level of funding. Innovative therapeutic approaches that emerge from this program will require large randomized comparative trials for confirmation. With additional fiscal and scientific support from NCI, Phase IIB/III studies could be performed in the proposed adult trials network.

Alternatively, comparative trials could be conducted in the COGs. However, the potential disadvantage of this approach is that these groups do not have the infectious disease expertise necessary for trial design and for integrated clinical management of HIV-related disease manifestations during the study.

4d. NIMH should be encouraged to support exploratory trials for the treatment of neurocognitive and psychiatric disorders in adults and children. In the future, comparative studies in adults should be conducted by the proposed integrated network with specific scientific and fiscal support from the NIMH.

4e. Every effort should be made to avoid competition and redundancy between the intramural and extramural programs. The intramural trials efforts should capitalize on the unique capabilities of the NIH Clinical Center and on the specific expertise of the sponsoring ICD. The Clinical Center provides the opportunity to bring patients to a single center for clinical investigation at no cost, including travel expenses, to the trial participants. This level of patient support is not routinely available even at excellent university medical centers with NIH-funded General Clinical Research Centers (GCRCs).

5. The Panel recommends that Institutes with a disease-specific (e.g., NCI) or an organ system-specific focus (e.g., NEI, NINDS, NIDDK) be responsible scientifically and fiscally for clinical trials specific to their mandate. Scientific priorities and consequent funding of the various intramural clinical trials efforts should be carefully scrutinized by each Institute Director.

The Panel carefully considered funding for NIH clinical trials, including both intramural and extramural programs. The need for a coordinated approach to extramural clinical trials is described above. While each Institute should define its own commitment to an intramural clinical trials effort, intramural trials should be designed to optimally exploit the unique resources of the NIH Clinical Center. Trials that do not take advantage of these resources and which are redundant with extramural and pharmaceutical efforts should be avoided.

Finally, the current appropriation for U.S. pediatric trials should be carefully scrutinized by the sponsoring Institutes and by the OAR coordinating group described above. The current level of support for the adult and pediatric ACTGs is nearly equivalent, although pediatric

cases are a small proportion of the HIV-infected population. The Panel recognized both the higher cost of pediatric trials compared with those for adults and a paucity of pharmaceutical industry resources expended on pediatric studies. Given the imbalance between the respective sizes of the adult and pediatric HIV-infected populations in the United States, the magnitude of funding for pediatric trials should be assessed on the basis of scientific and medical needs. The changing incidence of perinatal transmission may have a major impact on the total number of children available for studies. Thus, resources for the pediatric trials conducted in the United States, especially large, randomized Phase III efficacy studies, will need to be continually reassessed. The proposed OAR coordinating group should play a key role in this process.

A critical issue is to determine which scientific questions must be addressed in studies of HIV-infected children and what results can be extrapolated from adult trials. In the future, critical clinical trials for the management of pediatric HIV disease that require large pediatric populations may need to be shifted, at least in part, to the international arena. Extrapolations of results from clinical trials of new agents in adults would still need to be supplemented by studying pharmacokinetic and toxicity trials in children. The pediatric ACTG should emphasize Phase I safety and pharmacokinetic studies of antiretrovirals and antimicrobials for OIs, whether these are needed as a prerequisite to efficacy studies (in the United States or abroad) or as a guide to clinical use in children based on efficacy data obtained in adults.

6. **The Panel unequivocally supports the need for greater balance between investigator-initiated grants and targeted initiatives for support of clinical trials. Small-scale trials can and should be supported by individual grants.**

   This may require realignment of existing study sections to provide sufficient expertise for adequate review of such applications. Nonetheless, the Panel realizes that development of an adequate infrastructure for larger trials networks is crucial and will continue to require the allocation of targeted funds.

7. **Adequate and appropriate scientific review of proposed clinical trials programs—regardless of funding mechanism—must involve the most qualified, knowledgeable scientists.**

   Consideration should be given to the realignment of existing study sections that could be supplemented by an expert panel with defined terms of membership for the review of clinical trials networks, rather than the current ad hoc reviews assembled by the ICDs which may not have the requisite expertise. Increased inclusion of experienced HIV clinical trialists from outside the United States may be especially helpful when the majority of experienced U.S. investigators are also applicants.

8. **NIH and industry efforts should be coordinated. NIH studies should be undertaken that extend our knowledge of disease processes as well as assess the impact of therapy, which is typically not the focus of industry-sponsored trials.**

A distinction should be made between studies that would be performed by the pharmaceutical industry irrespective of the existence of an NIH clinical trials network and studies of greater scientific and medical relevance, such as trials to define optimal patient management for some aspect of HIV disease and trials to evaluate different therapeutic strategies. Cost-sharing arrangements with industry should be encouraged for the performance of collaborative studies.

9. The Panel did not dissect in detail the scientific agenda of each clinical trials program. These issues have been the subject of other targeted reviews. However, the Panel did recognize cross-cutting areas that should be of high priority. These include: (1) validation of surrogate endpoints as markers of clinical outcome, (2) utilization of aggressive combination therapies for all stages of HIV infection, including treatment of primary HIV infection (acute seroconversion), (3) elimination of HIV transmission from mother to fetus, (4) continued progress in the management and prevention of OIs, (5) HIV-associated malignancies, (6) HIV-associated neurologic complications, (7) immunologic interventions, (8) management of wasting syndrome, and (9) elaboration of the natural history components of therapeutic studies (e.g., mucosal shedding of HIV, the contribution of OIs to HIV progression, and long-term followup of unique cohorts of HIV-infected individuals who have participated in therapeutic studies). Furthermore, the feasibility of the interdigitating assessment of behavioral and medical endpoints should be evaluated.

10. **Better definitions of AIDS and AIDS-related research must be established so that AIDS funds are appropriately allocated. An improved database at the NIH is critical to both the management of NIH fiscal resources and the tracking of research progress.**

The basis for these recommendations appears in Section III.

II. Methodology

The Panel was constituted to provide broad representation of adult and pediatric infectious diseases expertise in HIV clinical trials, as well as individuals trained in other disciplines (neurology, oncology, statistics), scientists from the pharmaceutical industry, experienced HIV clinical trialists from outside the United States, researchers with expertise in related basic research areas (HIV virology, immunology, and opportunistic diseases), and community representatives. Diversity was sought with regard to academic discipline, gender, geographic location, community representation, and serostatus. (Appendix A contains biosketches and affiliations of all members and consultants.) The difficulties posed by assembling a knowledgeable review group entirely free of potential bias was recognized. The Panel adopted a policy of publicly identifying possible conflicts of interest or the appearance of such conflicts for members and consultants at the outset of the review process and at subsequent meetings. The Panel met six times, with the first meeting on May 3, 1995, and the last on November 13-14, 1995. (Appendix B contains the schedule of all meetings.) The final Panel meeting included a half-day open public session to receive testimony from individuals and groups wishing to provide input to the review process.

The AIDS Research Information System (ARIS) database for 1990-1994 was reviewed for all research projects according to the Strategic Plan codes for clinical trials (3B-3H), and corresponding abstracts were obtained from the NIH Division of Research Grants Computer Retrieval Information Systems Program (CRISP) database. ARIS was developed by the OAR to track AIDS and AIDS-related expenditures, so this review provided the initial description of NIH-funded efforts in clinical trials. The Panel subsequently targeted Fiscal Year 1994 for its review because there had been significant changes in funding from prior years, and because this was the most recent fiscal year for which complete data were available. Careful attention was paid to funds classified by the ICDs as AIDS or AIDS-related clinical trials research, but which were, in fact, directed to non-AIDS efforts according to the CRISP abstracts. (See Appendix D.)

The Panel was divided into six subpanels, primarily organized around the funding ICDs for the large, readily identifiable clinical trials programs. Each Panel member was assigned to two subpanels, and an attempt was made to match expertise to the programs to be reviewed. The Panel was thus divided into the following subpanels (with a chair named for each) at its first session (subpanel membership can be found in Appendix C):

- NIAID extramural adult trials
- Pediatric trials (NIAID, NICHD, NCI)
- NCI and NIAID (including collaboration with the NIH Clinical Center) intramural adult trials; NCI extramural trials
- NEI and NINDS trials
- NCRR programs
- Trials supported by other ICDs

Once programs were identified, written materials and presentations were requested of ICDs with key intramural and/or extramural funding in HIV/AIDS clinical trials: NIAID, NICHD, NCI, NCRR, NEI, NINDS, NIDDK, NIMH, and the National Heart, Lung, and Blood Institute (NHLBI), as well as from the NIH Office of Alternative Medicine (OAM). General and specific questions were submitted in writing to relevant NIH staff prior to the presentations, which were to focus on the goals, accomplishments, gaps, funding mechanisms, costs, and future directions of each trials program. Additional questions that arose from Panel discussions were subsequently addressed in writing to the appropriate ICD. The Panel assessed the publications record of the major programs for scientific impact and impact on the standard of care. The Panel also made use of prior scientific and administrative reviews that had been conducted by NIH and reviews by outside groups, including the Institute of

Medicine, Bishop-Calabresi* review of NCI intramural programs, Cassell-Marks review** of NIH intramural research, and advocacy groups such as Gay Men's Health Crisis (GMHC) and Treatment Action Group (TAG).

In addition to the retrospective evaluation, the Panel established principles by which the future needs of clinical trials research could be met and by which current efforts could be measured. An "ideal" clinical trials structure was defined to address the deficiencies of current clinical trials efforts and, more importantly, to provide a structure with flexibility to perform the required trials over the next decade. The advantages and disadvantages of a number of different funding mechanisms for trials of organ-specific disease processes associated with HIV infection, such as retinitis, or in broader subspecialty areas, such as oncology, were reviewed as possible models for collaborative support of clinical trials. The Panel's goal in reviewing these allied areas was to make optimal use both of fiscal support for research on specific manifestations of HIV disease and of scientific expertise of ICD staff.

A number of areas of overlap with other Area Review Panels were identified. These areas included the translation of the preclinical discovery process to the clinic, the therapeutic use of vaccines, the natural history of treated disease, the evaluation of alternative therapies, and the use of therapeutic interventions to increase our understanding of pathogenesis. In some instances, an overlap area was ceded to another Panel; in other instances, two or more panels addressed the issue from their unique perspectives, with subsequent discussion by the relevant panel Chairs and Executive Secretaries to ensure that an overlap area was fully addressed.

Through this process, the Panel developed a complete report from the work of the six subpanels, an Executive Summary of its findings, and recommendations. These were reviewed by the full Panel and submitted to the Evaluation Working Group.

III. Evaluation

A. Clinical Trials in HIV-Infected Adults

1. NIAID Extramural Effort: ACTG, CPCRA, DATRI, SPIRAT, MSG

Finding new and improved therapies for HIV-infected individuals is a critical global health priority. Among the NIH ICDs, NIAID has the lead responsibility for research on the treatment of HIV disease and its complications. There are many questions of great clinical and public health importance that can be answered only by well-designed and well-executed clinical trials. The first priority of the pharmaceutical industry is to license new drugs and to obtain expanded

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*"A Review of the Intramural Program of the National Cancer Institute," Ad Hoc Working Group of the National Cancer Advisory Board, June 26, 1995 (J. Michael Bishop, M.D. and Paul Calabresi, M.D., co-chairs).

**"Report of the Extramural Advisory Committee of the Director's Advisory Committee and the Implementation and Progress Report," Intramural Research Program, NIH, November 17, 1994 (Gail H. Cassell, Ph.D. and Paul A. Marks, M.D., co-chairs).

indications for approved agents. These priorities may or may not correspond precisely with priorities identified from scientific, clinical, or public health perspectives. Therefore, NIAID should support a clinical trials network with research capabilities ranging from small, intensive studies (including virologic and immunologic monitoring and Phase I studies) to large randomized, comparative Phase III/IV trials.

Scientific Priorities

The goal of NIAID's clinical trials research is to conduct studies that will have a significant impact on patient care and public health. This requires the capacity to perform different kinds of studies. The scientific leadership should avoid redundancy with industry-sponsored trials.

Strengths/Considerations

The NIAID extramural clinical trials effort has made significant contributions to the care and treatment of people with HIV disease. The initial clinical trials program, which ultimately became the AIDS Clinical Trials Group (ACTG), grew very rapidly under considerable pressure and public scrutiny. At the outset, a cohesive, well-directed clinical trials effort did not exist. The unanticipated early success of AZT forced the transformation of a group that had been selected to perform Phase I/II trials into a Phase III/IV network overnight. However, over the past decade the scientific leadership of the ACTG has developed and matured, bringing focus and direction to the network. Nonetheless, it is not surprising that, despite its many accomplishments, problems remain. Important issues that need to be addressed to optimize future productivity include the need for stable but flexible funding for a trials infrastructure that can answer the most important therapeutic questions in a timely fashion; scientific autonomy; and broad capability for studies ranging from small, laboratory-intensive pilot trials to large, randomized, comparative studies.

1) The current adult ACTG was initially funded by contract in 1986 as 14 AIDS Treatment Evaluation Units (ATEUs) to perform Phase I and II trials. The number of units was expanded to 19 in early 1987. Later that year, another 15 sites were funded by cooperative agreements (grants) as Clinical Studies Groups (CSGs), two of which were solely devoted to pediatric research, bringing the total number of clinical trials sites to 34. In 1988 the original contracts were changed to cooperative agreements, and the ATEUs and CSGs were melded into a single group, the ACTG, which was recompeted in 1991 and again in 1995. The ACTG is currently comprised of 30 units, of which 3 are designated as minority sites and are supported by set-aside funds. Some ACTUs function as tertiary referral sites, while others are clinic-based and provide HIV primary care. The early demographics of trial participants reflected those of the epidemic in the 1980s, consisting primarily of white gay men. Over time, the ACTG has demonstrated the ability to recruit a more heterogeneous pool of participants, with a demographic profile that has been reflective of the epidemic and very similar to that of the CPCRA in recent years.

   By the end of 1995, the ACTG had developed 281 trials, of which it had initiated 255, completed accrual for 177, and completed all patient followup for 142 (see Appendix E for a description of these terms). Since its inception in 1986 as the ATEU network, 47,108

cumulative patients have been enrolled, with 4,002 enrolled in calendar year 1995. Thirty-seven percent (193/542) of all adolescents in NIAID-sponsored clinical trials were enrolled by the adult ACTG. As of January 1996, there were 37 studies that were actively accruing.

The accomplishments of the ACTG are reflected in the 168 publications in first-rank journals (*Annals of Internal Medicine, Journal of Infectious Diseases, Journal of the American Medical Association, Journal of Pediatrics, Lancet, Nature, Pediatrics, Science*, and the *New England Journal of Medicine*), 120 papers in AIDS-specific journals, and many other numerous publications. (Definitions for first-rank and other journals are given in Appendix E.) These papers have addressed issues ranging from disease pathogenesis to diagnosis, use of surrogate markers for outcome, treatment of HIV infection and opportunistic diseases, and prophylaxis for OIs. It is reasonable to conclude that the ACTG has played a major role worldwide in defining therapeutic approaches to HIV infection and its sequelae.

The general contributions of the ACTG include the development of an infrastructure for the conduct of both complex intensive studies and large, comparative, multicenter Phase III trials; laboratory expertise in virology and immunology, including methodological advances and rigorous quality assessment; innovative approaches to clinical trials design and analysis; and the productive integration of people with HIV/AIDS and their advocates at all levels of the decision-making process. ACTG trials have largely defined the standard of care for HIV-infected adults, determining standards of therapy for HIV infection and for the prevention and management of OIs. The ACTG has also developed much of the methodology for clinical trials in these areas.

2) The Community Programs for Clinical Research on AIDS (CPCRA) awarded contracts to 18 sites in 1989 to expand Phase III/IV clinical trials into community-based settings and to reach patient populations that were underrepresented in the ACTG network at that time. In the first cycle of funding, 7 sites were designated as stage 2 (those with prior research experience) and 11 as stage 1 (those with no prior clinical trials experience that were providing primary care to HIV-infected individuals). The latter were afforded a 2-year period in which to hire and train staff and to acquire the necessary skills to conduct clinical trials. The CPCRA was recompeted in 1994 for a 5-year period and currently comprises 16 units.

   The CPCRA has developed 37 trials (32 interventional and 5 observational studies), of which 20 and 5, respectively, have been initiated. By the end of 1995, accrual had been completed for 16 interventional studies and all patient followup completed for 11 trials. The five observational studies have completed all patient followup. Since the inception of the CPCRA in 1989, 11,046 cumulative patients have been enrolled in interventional studies as of March 7, 1996, and 7,856 patients (42 percent) in observational studies, with a total of 1,634 enrolled in calendar year 1995. A total of 14 adolescents (2.6 percent of the total in studies) have been enrolled by the CPCRA and DATRI. CPCRA trials have included prophylaxis studies for various OIs, including one study aimed at preventing fungal infections in women and a number of Phase IV antiretroviral studies. As of January 1996, there were 4 studies that were actively accruing patients. The CPCRA has had 4

publications in first-rank journals and 21 methodological or AIDS-specific journal publications. Many of these publications were derived from analyses of the observational database.

The CPCRA has developed the ability to conduct clinical endpoint studies in a primary care setting and has demonstrated the ability to recruit a heterogeneous patient population from a variety of public and private clinical practice sites. It has an excellent record for patient retention and followup (see Appendix F). The CPCRA concentrates on clinical endpoint studies rather than trials that require intensive monitoring or laboratory-based endpoints. Data collection is streamlined to fit better into the primary care environment. For example, studies are designed so that all visits for all protocols occur on the same 3-times-a-year (every 4 months) schedule. Standards for data quality and timeliness are similar to, but less rigorous than, those of the ACTG. Some studies have been performed in collaboration with other programs (ACTG, Department of Defense [DoD]). This network has recently become involved in studies more complicated than was originally envisioned as the program's goal. The CPCRA statistical center has developed a patient-based database that facilitates cross-protocol analyses and longitudinal followup. The CPCRA has succeeded in recruiting and training a group of practicing physicians who otherwise may not have been involved in research. Natural history data from the observational database have been published. However, allowing for its later start and the more limited research experience of this group, its scientific productivity and impact on patient management have thus far been disappointing. From its inception, the CPCRA has integrated HIV-infected individuals with their advocates in all decision-making. This approach has played an important role in facilitating recruitment of participants from minority groups.

3) In response to external and internal reviews, the ACTG and the CPCRA have recently instituted significant changes in organizational structure. The effectiveness of these changes cannot yet be fully assessed. There are early indications that the timeline for protocol development in the ACTG, criticized as too slow and cumbersome, has recently improved. The recent reorganization of the CPCRA has resulted in significant movement of that group toward self-governance.

4) The Division of AIDS Treatment Research Initiative (DATRI) was funded by contract in 1991 to enable NIAID staff to mount studies to meet perceived research needs that were not being addressed by the ACTG and CPCRA. The DATRI contract was awarded to Westat, Inc., a commercial research organization that subcontracts with investigators to enroll patients. The scientific role of these investigators in the development or analysis of the trials is small to nonexistent.

   By the end of 1995, DATRI has developed 19 trials, of which it has initiated 11, completed accrual for 9, and completed all patient followup for none. Since its inception in 1991, cumulative enrollment has been 563, with 292 patients enrolled in calendar year 1995. DATRI resources have also been used to support pharmacokinetic substudies of two ACTG OI protocols. As of January 1996, these two substudies were the only studies actively accruing patients. There has been one publication in a first-rank journal thus far. Overall,

the Panel viewed DATRI as a failure. NIAID concurs and has decided that this contract will not be recompeted.

5) The Mycoses Study Group (MSG) is a NIAID contract-supported clinical trials mechanism based at the University of Alabama since 1978. Since 1988, 1,149 HIV-infected patients have been enrolled in MSG studies. Beginning in 1990, the MSG has received 50 percent of its support from AIDS funds because a significant proportion of its scientific agenda has been devoted to HIV-associated fungal disease. NIAID support is used for personnel and infrastructure costs at the MSG central unit and for support of the four subproject leaders. Forty-eight site investigators receive no patient or other cost reimbursement from the MSG except for travel to the annual meeting. Funding for the actual conduct of studies is sought from pharmaceutical sponsors; per-study costs have ranged from approximately $1.5 to 5 million. Although this has been a very cost-effective way for NIAID to address public health needs (the average per-capita cost supplied by industry is $4,700), this dependence on industry support has at times had an impact on study design. Other than its reliance on industry for support of specific studies, this NIH-academia-industry collaboration may serve as a model for a clinical trials mechanism.

   The MSG is jointly managed by staff from the NIAID Division of Microbiology and Infectious Diseases (DMID) and the Division of AIDS (DAIDS). The four MSGs subprojects are structured around four pathogens or groups of pathogens: (1) *cryptococcus*, (2) the endemic mycoses (histoplasmosis, blastomycosis, coccidioidomycosis), (3) *Candida*, and (4) *Aspergillus*. To date, there has been no prioritization across these different pathogens. Studies in HIV-infected patients have been conducted in concert with the ACTG OI effort since 1987. Collegial interactions among MSG and ACTG investigators have been facilitated by efforts to ensure cross-representation between the two groups at scientific planning and decision-making levels. The contributions of the MSG-ACTG collaborative effort to the management of systemic fungal disease have been substantial. MSG studies have defined the standard of care for the management of AIDS-associated cryptococcal meningitis, disseminated histoplasmosis, and coccidioidomycosis.

6) The Strategic Program for Innovative Research on AIDS Treatment (SPIRAT) was initiated in 1994. This program emphasizes therapeutic approaches to HIV that do not involve conventional antiviral drugs, including the use of novel high-risk therapeutic approaches (gene therapy, cellular immunotherapy, ribozymes, etc.) that have not yet been successfully implemented for any disease. This academic-industry collaborative effort supports late-stage preclinical development and early proof-of-concept clinical trials. Thus far, nine trials have been developed, of which three have been initiated. Total cumulative enrollment since SPIRAT's inception is 18 patients, all of whom were enrolled in 1995. It is too early for the Panel to make a thorough assessment of this program. Unique attributes that are not now apparent may emerge in the next few years. However, the Panel was concerned that the initiative's required timeline for beginning pilot studies narrowed the pool of competitive applicants, and that planning is inadequate for translation of a successful proof-of-concept study from this program into the larger clinical trials networks.

7) The Division of AIDS, the adult ACTG, and the CPCRA have collaborated effectively with other clinical trials networks. The ACTG has worked with other NIAID-sponsored programs (such as the Mycoses Study Group and the Collaborative Antiviral Study Group), as well as with the U.S. Centers for Disease Control and Prevention (CDC) and various international research networks such as Pan American Health Organization (PAHO) in Latin America, INSERM in France, and European, Canadian, and Australian investigators sponsored by industry. These collaborations have largely targeted the treatment and prevention of OIs, such as prophylaxis for tuberculosis, *M. avium* complex, toxoplasmosis, and cytomegalovirus, and the treatment of cryptococcal meningitis, disseminated histoplasmosis, varicella zoster virus infection, and toxoplasmosis. The ACTG and CPCRA have collaborated on TB treatment studies and with the CDC and PAHO on a large TB prevention trial; however, these efforts have had limited success in enrolling the required numbers of patients. Both have also collaborated with the DoD on various antiretroviral and OI trials. The potential benefits of these interactions are obvious, particularly with regard to the opportunity to perform collaborative studies rather than to undertake competing trials.

8) The adult ACTG and CPCRA provide important training opportunities for clinical investigators in HIV and associated infectious diseases. The ACTG is the major vehicle for such training in the United States. Young investigators have had opportunities to learn clinical trials design and management, serve on protocol teams, chair studies, and ultimately to assume leadership positions, but access to these activities has been uneven across the different research committees. The CPCRA has trained primary practitioners in the design and conduct of randomized, comparative clinical trials.

Opportunities

1) With the scheduled recompetition of the ACTG and CPCRA in 1999, NIAID has an important opportunity to reevaluate the structure of its adult clinical trials networks for HIV/AIDS. There is sufficient time before the next funding cycle to assess the effect of recent organizational changes in the existing programs and to adequately design a flexible, integrated network. In the interim, the creation and utilization of external scientific advisory boards for each program should ensure appropriate direction.

2) The existing NIAID trials effort is well-positioned to conduct important studies that will have a significant impact on public health, including combination antiretroviral studies and studies of OI prophylaxis. There are key opportunities to conduct studies which are not likely to be conducted by industry, especially the comparison of combinations of agents from different companies. It is essential to conduct trials, based on a sound scientific agenda, that are relevant to the public health.

3) There are opportunities for new investigative initiatives in the treatment of acute HIV infection.

4) There are valuable opportunities to design trials so that the pathogenesis of AIDS and its associated complications (opportunistic diseases, wasting) can be studied in the context of therapeutic and prophylactic interventions.

5) NIAID can initiate and ensure cooperation among the existing clinical trials networks, as well as with industry, international research groups, and disease-related clinical trials efforts centered in other ICDs.

Needs

A clinical trials network is needed that is capable of conducting a range of clinical trials, and that encompasses a range of diverse research sites (academic as well as community practice venues) with access to demographically and geographically diverse patient populations. There is currently no scientific justification for separate trials networks based solely or primarily on the clinical setting in which patients receive care; although ACTUs are based at major medical centers, many of these sites provide primary care. This is borne out by the fact that current overall demographic characteristics of the ACTG and CPCRA networks are very similar. Potential advantages of a network that encompasses diverse research sites would include the combined insights from both research and practice perspectives on the critical questions to be answered, and improved access to the full range of HIV-infected subgroups. Features of an optimal network already exist (in part) among currently funded networks. The Panel recommends a model for an optimal future clinical trials program that embraces all of the current adult NIAID clinical trials programs (adult ACTG, CPCRA, and, possibly, SPIRAT). The Panel considered and rejected the concept of multiple, competing trials networks like the cooperative oncology groups. HIV/AIDS trials pose unique challenges. While acknowledging the value of competition, the Panel was wary of splintering the necessary sophisticated laboratory support, hindering access to sufficient numbers of patients for studies of opportunistic diseases and for standard-of-care trials which require very large sample sizes, and creating harmful competition for access to new agents.

The proposed network's structure would permit the flexibility to conduct clinical and laboratory assessments within a given study at varying levels of intensity. For example, within a large randomized Phase II or IV trial, resource-intensive virologic, immunologic, and clinical substudies that will provide important insights can be performed by core facilities on a subset of participants. Flexibility requires the ability to efficiently increase or decrease the number and size of research sites for the largest Phase III and IV trials. A set of core sites with the research capabilities at some current adult ACTUs would be maintained to conduct Phase I and IIA studies with intensive virology, immunology, and pharmacology laboratory components. Such sites would have stable funding through a grant mechanism. These sites might also participate in larger Phase IIB and III trials. At the next level, sites capable of designing and performing intensive clinical investigations typical of Phase IIB and III studies, such as some current ACTG and CPCRA units, also would require stable funding through a grant mechanism. Access to large numbers of demographically diverse populations for the conduct of Phase IV and some Phase III trials, with streamlined data collection and less intensive monitoring, will be important to meet research opportunities, particularly optimal standard-of-care trials. Sites capable of successfully performing these studies, such as some CPCRA and a few ACTU sites,

could be supported by a contract mechanism that would permit rapid scale-up and contraction to meet changing research opportunities. The contract mechanism used by NICHD to support some of the pediatric sites may be a useful model, as described below. Lastly, a contract mechanism may also be used to support the participation of individual practitioners who are qualified to serve as investigators in specific Phase IV studies. These clinicians would be required to meet the network's specified qualifications. This level of research capacity might involve, for example, the registration of patients into a large, relatively simple trial by calling a toll-free number. The following elements also are important to the functioning of the proposed network:

1) The network should be open to the participation of qualified investigators. Investigators could participate in two ways: scientific contributions and participation in Phase IV (optimal management strategy) trials. This includes the potential for contributing scientifically through the submission of concept sheets for proposed studies. To enroll subjects in studies, investigators would be expected to demonstrate that they can meet network standards for the conduct of high-quality research at the proposed level of intensity. Because Phase IV trials focus on marketed agents and limit laboratory testing to that required for patient management, and because data collection will be minimal, this might entail limited or no financial compensation using a contract mechanism.

2) NIH-sponsored trials should not compete with pharmaceutical company trials. The NIH should concentrate on performing studies that will lead to improved treatment and to better define disease pathogenesis. Specifically, the NIH trials effort should be strongly discouraged from committing resources to studies that would normally be conducted by industry for licensure. Dialogue between industry, the proposed federally funded trials network, and the proposed coordinating group will be required to define the roles of each in the clinical trials process. Cost-sharing arrangements with industry should be encouraged for the performance of collaborative studies.

3) Leadership of the proposed network must come from investigators whose research has been peer-reviewed, working in collaboration with investigators supported by other ICDs.

4) It is essential that the proposed trials network have a standing mechanism for independent external scientific review and advice. This external review board, appointed by the network leadership, should be comprised of experts who are not funded by the network. The recently created Scientific Advisory Board of the ACTG may be a model for such independent input.

5) NIAID program staff should have two key roles in the network:

    a) Ultimate scientific authority should reside with the network leadership that has been assessed by the peer review process. Program staff should participate in all scientific decision-making as voting members of the appropriate committees but should not be able to exert veto power. It should be recognized that, under unusual circumstances involving legal and ethical issues for which the Government may be held responsible, it may be appropriate for ICD staff to exercise the power to veto a study. Regulatory

and scientific reviews by program staff should be conducted in a timely fashion, so that their input is available to the scientific leadership at the time of final decision-making. Staff input should ensure that the network is responsive to national needs.

b) Once scientific decisions have been made, the appropriate role of ICD program staff is to facilitate implementation. These responsibilities include timely coordination with other ICDs and other Federal agencies as indicated, exercising regulatory responsibilities in a manner that is collegial and user-friendly, and facilitating interactions with the pharmaceutical industry. This latter role may become increasingly important as cost-sharing is implemented.

6) Given its importance as a national resource and the inherently expensive nature of therapeutics research, appropriate peer review for clinical trials networks must involve the most qualified, knowledgeable scientists. There is evidence of unevenness and bias in past reviews. Consideration should be given to the reorganization of current study sections to include appropriate expertise in HIV/AIDS clinical trials, rather than reliance on the current *ad hoc* review panels, which are assembled by the individual ICDs and may not have the requisite expertise. Increased inclusion of experienced HIV/AIDS clinical trialists from outside the United States may be especially helpful when the majority of U.S. investigators are applicants.

7) HIV is a multisystem disease. HIV clinical trials, therefore, require the scientific input of ICD program staff and outside investigators in allied disciplines and require better scientific coordination among the involved ICDs. All Institutes involved in these trials should fully utilize the resources for the conduct of Phase IIB/IV trials, rather than create new redundant, expensive trials mechanisms. All available funding mechanisms should be used creatively by these Institutes to help support the infrastructure of the NIAID-sponsored network.

8) Appropriate support for essential components of a successful trials network include the following: data management and statistical support; an operations center; quality-controlled virology, immunology and pharmacology laboratories; appropriate support for laboratory expertise in opportunistic pathogens; a specimen repository; adequate field monitoring; and a central administrative core. Clinical trials databases should be structured to facilitate data sharing and meta-analyses.

9) There is a need to define the health care issues related to HIV infection that require subpopulation-specific and gender-specific investigation.

10) Swift dissemination of key clinical trial results, including timely publication, must be ensured.

11) Clinical trials mechanisms that have not been sufficiently productive, such as DATRI, should be phased out. Although NIAID has determined that DATRI will not be recompeted, at issue is the question of whether support for completion of ongoing and planned DATRI trials is warranted. The Panel recommends that such support be reviewed

on a case-by-case basis. Trials that have not yet been initiated, such as the oral interferon-alpha study, should not be supported by administrative mechanisms and undergo independent external peer review. This review could be accomplished by the clinical trials coordinating group previously described.

2. NIAID Intramural Effort (Including Collaboration with the NIH Clinical Center)

The NIAID intramural program is conducted in close collaboration with investigators from the Department of Critical Care Medicine at the NIH Clinical Center. This program is under the joint leadership of Drs. H. Clifford Lane (NIAID) and Henry Masur (Clinical Center) and includes basic and applied laboratory research components and clinical research. Clinical research performed by NIAID and Clinical Center investigators encompasses both natural history studies and clinical trials, and clinical trials have evaluated new drugs for HIV and OIs including a focus on the investigation of immunologic approaches to therapy for HIV, especially interferon and interleukin-2 (IL–2). As with other intramural programs, the NIAID and Clinical Center efforts undergo outside review every 4 years by their respective Boards of Scientific Counselors.

Scientific Priorities

The stated goal of the clinical trials broad program is to perform novel studies that explore pathogenesis, diagnosis, and therapy of HIV disease and its complications and that will not be in competition with either pharmaceutical company efforts or those of the extramural clinical trial programs of the Institute. The program emphasizes immunologic approaches to therapy of HIV infection and the treatment and prevention of OIs.

Strengths/Considerations

1) Studies performed by the NIAID intramural/Clinical Center team encompass a range of clinical investigations, of which therapeutics research is one component. Since 1983, a total of 146 protocols have been developed (enrolling a cumulative total of 3,800 patients), for which 75 are clinical trials of which 73 have been initiated. By the end of 1995, data regarding the number of studies with all accrual completed (110) and all followup completed (103) include the full range of clinical studies. These clinical trials are not restricted to studies of therapeutics. In calendar year 1995, there were 223 new participants entered into the full range of clinical studies. As of January 1996, there were 11 studies actively accruing participants.

2) The intramural investigators have been very productive, with 46 articles that describe the principal and secondary findings of clinical trials focused on therapeutics; these represent a subset of a much larger total number of publications (393) in diverse areas, including pathogenesis, natural history, diagnosis, case reports, preclinical research, reviews, and consensus articles on treatment and preventive therapy. Of the papers derived from therapeutic trials, 27 have appeared in first-rank journals and 19 in AIDS-related or specialty journals.

3) The intramural programs of the NIH provide a unique environment for the performance of human investigations.

4) Intramural and extramural budgets are difficult to compare due to differences in accounting methods. Intramural budgets include the costs for the Clinical Center, the maintenance of the NIH campus, and the funding for accounts that support both laboratory and clinical research, including support for clinical trials and patient travel. The total annual budget for the NIAID intramural clinical trials program is $15.8 million; approximately $3.9 million is allocated for antiviral trials, $8.7 million for immune-based therapies, and $3.1 million for OIs. The recent Cassell-Marks report on NIH intramural research recommends support for the current structure with its attendant expenditures. The Panel respects the efforts of the Cassell-Marks panel in its prior review and wishes to ensure continued oversight by the Institute Director for the best use of these intramural research funds.

Opportunities

1) The joint NIAID/Clinical Center intramural program should continue to focus on the special expertise of the investigators and the unique resources provided by the Clinical Center. These areas include the investigation of immunophysiology, immunopathology, and pathogenesis including the studies of lymph nodes and discordant twins.

2) The investigators should continue to redirect their efforts away from those Phase I/II studies of drugs for HIV and OIs that are now routinely conducted in most medical centers, and focus on those types of projects that make use of their strengths and capabilities.

Needs

The Panel supported the approach taken by the intramural leadership to shift priorities and to perform trials in a way that complements other programs. No recommendations for major changes in direction were made.

3. NCI Intramural Effort

The NCI, which has a new Director, has recently undergone extensive review of its intramural program (the Bishop-Calabresi Report) and has lost several major AIDS investigators. As would be anticipated, within NCI, a reevaluation of its role in AIDS research is well under way.

Scientific Priorities

The NCI intramural program on HIV in adults, under the leadership of Dr. Robert Yarchoan, has made significant contributions to AIDS clinical research, including the first demonstration of the antiretroviral activity of nucleoside analogues, the early development of dideoxynucleosides, the impact of zidovudine (AZT) on HIV-associated neurological disease, the benefits of combination therapy, and the role of lymphocyte activation in nucleoside antiviral activity.

Strengths/Considerations

1) By the end of 1995, the NCI intramural team had developed 28 trials, of which it has initiated 25, completed accrual for 20, and completed all patient followup for 16. Since 1984, a cumulative total of 532 patients have been enrolled, with 48 enrolled in calendar year 1995. As of January 1996, there were four studies actively accruing patients.

2) The intramural investigators have been very productive, generating a total of 26 primary, 43 secondary, and 36 review articles. Of the 69 primary and secondary articles, 27 have been published in first-rank journals, and 42 in AIDS-related and subspecialty journals.

3) Despite its relatively modest size, this program has been successful. It has the advantage of flexibility to act with speed and innovation. Total costs for 1994 were $3 million, which includes Clinical Center overhead. These costs are clearly justified by the scientific impact of the program.

Opportunities

1) The Panel strongly recommends that future efforts focus on areas to which NCI brings unique expertise, as exemplified by: (1) Phase I/II studies of novel cancer chemotherapeutics, such as angiogenesis inhibitors and paclitaxel, (2) continued collaborations with other NCI intramural scientists on immunologic studies, and (3) Phase I/II studies of drugs that have been developed by the NCI preclinical drug discovery program (such as KNI-272 and zinc finger-binding compounds).

2) Recent efforts on Phase I/II studies of new antiretroviral drugs, such as 3TC, should be refocused on studies that use the unique resources of the NIH Clinical Center and on innovative research on AIDS-associated malignancies to which this group has recently committed, such as the Phase I trial of angiogenesis inhibitor for Kaposi's sarcoma.

Needs

No recommendations for major changes in direction were made.

4. NCI Extramural Effort

a. Scientific Priorities

NCI's Clinical Therapeutics Evaluation Program (CTEP) has issued several initiatives relating to the treatment of AIDS-associated malignancies, the support of clinical trials, correlative clinical studies (AIDS malignancy tissue banks), and more basic research investigations on disease pathogenesis. More recently, CTEP also has encouraged the development of trials within the various established Cooperative Oncology Groups (COGs); these studies appear to be accruing well. A new AIDS Malignancy Consortium (AMC) was established in 1995 to carry out Phase I and II studies of innovative therapies. The Panel noted that, historically, most of the AIDS malignancy treatment research has been conducted by the adult ACTG.

The Panel was concerned about the commitment of a significant amount of "AIDS" and "AIDS-related" research dollars by NCI to non-AIDS-related research.

Strengths/Considerations

1) The staff of NCI and its extramural investigators are uniquely qualified to provide leadership in the evaluation of therapies for AIDS patients with malignancies. The AMC has the potential to be a driving force in studying innovative treatments for AIDS-associated malignancies.

2) Historically, the NCI support of therapeutic trials on AIDS-associated malignancies has been inadequate. As a result, NIAID assumed the direction and costs of such trials. As a consequence, the responsibility to evaluate therapies for opportunistic malignancies will require significantly increased participation and funding by NCI.

3) The Panel noted that a substantial portion of NCI extramural funding has been classified as AIDS-related. In many cases, the relationship between the funded projects and AIDS-related malignancies was not apparent to the Panel.

Opportunities

1) NCI should use the reorganization of its AIDS research program to redefine its mission and to assume a leadership position regarding clinical trials of AIDS-related malignancies. NCI program staff and the extramural oncology community have the opportunity to lead the worldwide biomedical community in this area.

2) The reorganization also offers the opportunity to provide adequate funds to support this mission. Funding for the AMC should be sufficient to cover patient costs, including administration of investigational agents, and assays to measure various virologic, immunologic, and other biologic parameters. Every effort should be made to link the AMC with the current ACTG/future NIAID network to optimize patient referral; to expand patient access to and enhance patient accrual in all HIV clinical trials; to include infectious disease expertise for optimal patient management; and to use the ACTG's existing laboratory resources for virologic and immunologic assays rather than to create its own resources in these areas *de novo*.

3) Proper classification of funds for AIDS and AIDS-related research (see Strengths/Considerations 3 above) should permit reallocation of adequate funds to accomplish these objectives. The Panel noted that a large proportion of NCI extramural funds classified as AIDS-related clinical trials are supporting studies that are unrelated or distantly related to AIDS. These funds should be redirected in part to strengthening the AMC and the nascent AIDS efforts within the established COGs and to supporting the infrastructure of the NIAID network for larger randomized Phase IIB/III trials of promising agents investigated by the AMC.

4) The translation of basic scientific findings and the introduction of new drugs into clinical trials will require special coordination and cooperation of NCI and NIAID to integrate the activities of their trials. Nevertheless, the opportunity to study HIV disease pathogenesis in concert with oncogenesis is unparalleled.

5) A mechanism should be established between NCI and NIAID to fund state-of-the-art HIV-related immunologic and virologic assays of specimens from patients enrolled in AMC and COG studies at certified ACTG laboratories.

Needs

1) The leadership of NCI should clearly define the Institute's role in the performance of clinical trials in AIDS-associated malignancies. The recently awarded AMC is now in place and can be used to support the mission of the Institute with regard to pilot trials and early-phase innovative therapeutic trials.

2) The resources presently allotted to the AMC are inadequate to perform Phase I/II clinical trials that are both labor-intensive and laboratory-intensive.

3) Provision should be made for the performance of Phase III studies. This goal might be achieved through the established COGs and/or through oncologists at ACTG sites. Rather than commit a large amount of fixed funds to a separate AIDS oncology trials network for comparative Phase IIB/III trials, a flexible mechanism should be established to permit an *ad hoc* response to scientific opportunities that builds upon established NCI and NIAID programs. This might be funded by a master contract mechanism similar to that used by the NICHD to co-fund with NIAID the pediatric ACTG. Such a mechanism would provide support for the accrual of patients into studies by the COGs, ACTG, or other qualified investigators. The Panel expressed concern that the COGs would be the most appropriate clinical trial settings for randomized, comparative studies of AIDS-associated malignancies. The COGs lack the expertise in infectious diseases necessary for optimal study design and patient management with regard to the underlying HIV disease and its infectious complications. The AMC, COGs, and other future NCI-funded trials would be strengthened by support for formal interaction with NIAID-supported investigators and laboratories (such as the ACTG virology and immunology committees and laboratories). This also might include membership on key committees and working groups in the NIAID adult network, travel to network meetings, and funds for necessary virologic and immunologic testing to assess the impact of anticancer agents on the course of HIV infection.

B. Clinical Trials in HIV-Infected Children

1. Joint Extramural Program of NIAID/NICHD

NIAID and NICHD are now inextricably linked in their support of the pediatric AIDS clinical trials effort; therefore, the pediatric ACTG program will be considered in its entirety. In FY 1995, these efforts were funded at a level of about $70 million.

Scientific Priorities

1) The highest priorities of the pediatric ACTG are studies aimed at interruption of perinatal (vertical) transmission of HIV infection and early therapy of infected babies, from the time of exposure of the infant to maternal virus. Such studies may include administration of treatment during pregnancy/labor, delivery, and to the newborn.

2) HIV-infected neonates are a unique population for early antiretroviral intervention because the time of HIV acquisition can be defined. An important priority is to evaluate whether early therapy can alter the subsequent course of disease. This and other questions of scientific significance, beyond the pediatric population alone, may be addressed in both adults and children or preferentially in the pediatric population, where the answers may be reached more quickly.

Strengths/Considerations

1) In 1986, three sites received ACTG funding for pediatric studies. By 1989, a total of 15 sites were supported, and 9 more sites were funded in 1991 in response to a Congressional mandate. These 24 NIAID-funded units, supported by cooperative agreement (grants), will be competitively renewed in 1996.

   The NICHD pediatric sites were initially funded in 1988 through a master contract mechanism to perform a single multicenter trial of intravenous immunoglobulin therapy. When the decision was made to include NICHD-funded sites in the pediatric ACTG, contract support was extended to 27 sites to enroll patients in the full range of pediatric ACTG studies. These sites are reviewed by the contractor and NICHD program staff but do not submit grant applications for NIH peer review. Internal standards for quality control permit eliminating or adding sites within a 6-month timeframe, thereby offering significant flexibility for the pediatric network as a whole by funding capable sites that already manage HIV-infected children.

2) Although it took time and the firm commitment of the respective Institute directors, the combined NIAID/NICHD infrastructure is now well established. The unique elements of the combined resources from the two Institutes, with cooperative governance by the respective program staff, form a single functional unit and constitute a model for other inter-Institute collaborative efforts.

3) By the end of 1995, the pediatric ACTG had developed 73 trials, of which it had initiated 56, completed enrollment for 32, and completed followup for 8 studies by the end of 1995. As of January 1996, there were 13 studies actively accruing patients. Cumulative enrollment since 1987 totals 8,836, with 2,119 patients enrolled in calendar year 1995. A total of 542 adolescents have been enrolled in trials, almost all of them (528) in five specific trials, two of which are observational studies. Of these 528 adolescents, 335 (61.8 percent) were enrolled at pediatric ACTG sites, with two-thirds of them at NIAID-funded units. The remaining 193 (35.6) percent were enrolled at adult ACTG sites.

The success of the pediatric ACTG is reflected in the publication of 62 articles in first-rank journals and 80 articles in AIDS-related and subspecialty journals.

4) The pediatric ACTG, together with the NCI intramural program, have defined the standard of care for HIV-infected children.

5) The pediatric ACTG has been able to enroll pregnant women (with assistance from adult ACTUs), neonates, and infants in trials. ACTG 076, which demonstrated a 66 percent reduction in the rate of HIV transmission from asymptomatic mothers to their infants with AZT use, was a complex perinatal trial with a critically important outcome. The implementation of the recommendations from ACTG 076 should significantly decrease the incidence of vertically transmitted HIV infection.

6) It is possible that, ultimately, fewer children will be infected, and, although pediatric disease will still occur, there may not be a sufficient number of patients for a randomized, comparative Phase III trials program in the United States. Unfortunately, this prospect is unlikely in developing countries. It may be necessary to shift the focus of pediatric therapeutics research to the international setting, although there still will be a critical need for careful Phase I pharmacokinetics and toxicity studies that perhaps can best be conducted in the United States.

7) In addition to the two lead Institutes, other ICDs, notably NHLBI and NIMH, have supported specific ancillary costs of pediatric ACTG studies, e.g., by providing hyperimmune anti-HIV intravenous immunoglobulin (HIVIG) for a perinatal transmission study and supporting neurodevelopmental studies.

8) Pediatric ACTG trials have been very costly: approximately $9,000 per patient in 1995. This cost does not include NHLBI and NIMH support. This increase has been justified on the basis of the range of needed support services to engage mothers and children in the clinical trials system. Intensive laboratory monitoring is also a factor. Nonetheless, attention should be paid to making these studies as cost-effective as possible. Some additional considerations include:

   a. Several elements having lower priority might be eliminated. One example is the NIMH component that supports a single study assessing developmental neuropsychologic examinations. This trial, begun in 1992, is half-accrued at an annual cost of $2.5 million and is projected to run for 3 more years. Although the results may ultimately yield different methods for assessing development in infants, existing tools have been used successfully in ACTG trials and the lengthy examinations being evaluated may be impractical for broad use. The total expense is difficult to justify; therefore, the Panel recommends that this study be closed to accrual and that the available data be analyzed.

   b. At the end of 1995, approximately 3,000 patients were being followed on studies, with about 2,000 of these patients at NIAID sites and 1,000 at NICHD sites.

c. Within the pediatric ACTG, the relative numbers of patients enrolled through the two mechanisms would seem to indicate that the NICHD-funded sites are somewhat more expensive than the NIAID-funded sites. In 1995, the total expenditures for the NIAID and NICHD components were $33 and $24 million, respectively (excluding the modest NIMH and NHLBI contributions described below). Since the NICHD sites began active patient recruitment in 1990, these sites have enrolled 31 percent (2,750) of the cumulative total (8,905) patients, including 42 percent (625) of all new enrollees (1,500) in 1995.

   For NICHD sites, which are funded by subcontract from the master contractor, baseline funding is individualized; patient costs are negotiated initially and then billed after study visits occur. The flexibility of this mechanism, within a 6-month timeframe, provides a means to add sites or discontinue support in months. It is essential to examine critically: (1) the current number of sites funded and their relative costs to determine whether the number of sites could be reduced; (2) the funding formulae used to determine whether the system is capable of greater efficiency, e.g., routine trials and perinatal trials with monthly visits have been allocated one staff position per eight patients, and observational studies have been allocated one staff position per 25-50 patients; and (3) the cost per patient according to the type of study. Per-capita annual costs are highest for perinatal and Phase I studies ($7,000-9,500) and usually lower for Phase II/III trials ($3,000-4,500).

d. Any future decrease in total support for the pediatric clinical trials network must consider that this network, while supported by two Institutes using different funding mechanisms, is a single functional entity.

9) The pediatric ACTG provides a training opportunity for pediatric clinical investigators in infectious diseases/HIV and is the major vehicle for such training in the United States.

Opportunities

1) The recognized exposure of a newborn infant provides a targeted time for the early treatment of HIV infection that could alter the subsequent course of disease.

2) Because disease progression is typically rapid in perinatally infected children, early treatment of this group may provide answers more quickly as to the value of early therapeutic intervention in HIV infection in general and the relationship of clinical disease progression to virologic and immunologic markers. This opportunity depends on whether pediatric cohorts of sufficient size can be enrolled swiftly.

3) The opportunity exists for continued progress in preventing perinatal transmission through the exploration of drug combinations to improve the current AZT monotherapy outcome. Appropriate studies may be required in the international setting, where high rates of HIV transmission to newborns continues.

4) The pediatric ACTG has the continuing opportunity to provide the necessary pharmacokinetics and initial safety data for the use of new antiretrovirals and antimicrobials for OIs in pregnant women, neonates, and infants, even in the event of a waning U.S. epidemic. Pharmacokinetics studies in neonates are essential because drug metabolism is so different in the first few weeks of life. Such Phase I studies are the necessary prerequisite to trials, whether they are conducted in the United States or abroad. These studies are essential if therapeutic agents studied in adults will be used to manage HIV-infected children, since dosing and drug formulations may be different in children.

5) Enhanced collaboration between the pediatric ACTG and the pediatric intramural NCI program provides opportunities for investigating new agents, optimal drug combinations, and therapeutic strategies for the management of HIV and its complications.

6) Clinical trials for children provide a unique opportunity to bring infected mothers into both health care delivery and clinical research programs.

7) Although there is an available population of infected adolescents to enter clinical trials in both the pediatric and adult ACTG networks, there is presently no defined need for a major investment in trials specifically targeted to this group.

Needs

1) The enormous fiscal commitment to pediatric trials in the United States must be examined for appropriate magnitude and cost-effectiveness. It is certainly plausible that pediatric trials could be performed at a lower total cost. This commitment should be reevaluated at regular intervals in the future to determine whether recent indications of population-based reductions in perinatal transmission rates will be sustained. The need for a continued U.S. Phase III clinical trials program needs to be balanced against the possibility that antiretroviral use may significantly decrease perinatal transmission, making large randomized trials in the United States more difficult to conduct. It may require that capability for conducting Phase III/IV trials outside the United States be included in planning.

2) The paucity of pediatric formulations limits the early development of new drugs for use in pregnant women, infants, and children. This may be due to liability concerns and a lack of financial incentives for pediatric formulations. Concerted efforts should be directed toward encouraging the earliest possible development of such formulations. Both the NIH and the Food and Drug Administration (FDA) should encourage industry to develop appropriate formulations so that development of therapies for children, infants, and pregnant women can proceed in tandem with therapeutic research in adults.

3) Although the number of infected children may decrease in the United States, it is highly unlikely that this decrease will occur in the developing world. Phase I studies in newborns and pregnant women will be crucial to the continued development of regimens to interrupt transmission. Phase I studies in older children also will be crucial to advances in clinical management of HIV disease, particularly if the results of studies in adults are extrapolated

to children in the absence of specific studies in the pediatric population. It is critical to have the capability to continue conducting such trials in the United States.

4) There is no existing mechanism within NIAID to determine whether questions of broad scientific interest, such as treatment of newly acquired infection, should proceed either preferentially or at least initially in adults or children. Adult and pediatric clinical trials programs should be coordinated by the proposed group.

5) Competition between the NCI intramural pediatric program and the pediatric ACTG for drugs entering Phase I trials makes it imperative that the two programs delineate responsibilities for the performance of these studies so that they can be accomplished as quickly as possible. In particular, data are needed for the use of agents for treatment of OIs in infants and children.

6) The current projected enrollment of 2,000 to 3,000 patients per year appears optimistic. A more realistic approach to what actually can be accomplished in pediatric therapeutics should be developed, and studies must be designed and scaled to realistically achievable enrollment levels. A means of evaluating existing studies should be established as soon as possible and clinical trials assessed for their potential contribution to overall scientific goals. Studies with lower priority that duplicate adult trials should not be initiated; those already under way should be halted, especially studies that have poor accrual or are scientifically outdated. New studies should focus on the evaluation of drugs that are truly critical to the management of children so that the requisite pharmacokinetics and safety information can be obtained.

7) There have been prolonged delays in initiating some studies. Although this is a multifaceted problem, and some progress has been made recently, it is essential to ensure timely initiation and rapid completion of studies. There is a need to accelerate protocol development, make the use of pediatric clinical trial resources more attractive to industry, and avoid competition for the same drugs.

8) Barriers to clinical trials participation by the growing number of infected adolescents should be identified.

9) Access of HIV-infected mothers to clinical trials aimed at improving the management of HIV disease in adults must be improved, whether through facilitated referrals to trials in the adult network or through access to such studies conducted at pediatric sites. Historically, opportunities to enroll infected mothers have been missed because of the separate mandates, goals, and locations of adult and pediatric research units. The proposed coordinating group should provide oversight of access to adult trials for infected mothers.

10) The possibility that infected women will be enrolled in perinatal transmission studies and in studies for the management of HIV disease in adults underscores the need for clinical trials databases with key standardized elements. Incompatibility between these datasets will limit the ability to assess the full impact of therapeutic intervention in childbearing women.

2. NCI Intramural Pediatric Program

The NCI intramural pediatric program, under the leadership of Dr. Philip Pizzo, has developed an outstanding program for the conduct of Phase I/II trials. NCI's participation in the initial ACTG 003 trial of AZT contributed to approval of the drug for use in children. NCI investigators conducted the initial pharmacokinetic studies of ddI and 3TC in children, 3 months of age or older.

Scientific Priorities

The priorities of this program have been tailored to the accessible patient population, which is largely composed of older children with established disease, many of whom have received prior therapy. Pharmacokinetics studies, antiretroviral therapy of advanced disease, and use of agents for OIs have been areas of emphasis. Other aspects of this program include observational psychosocial and neuropsychological studies that do not involve investigational therapies and are observational in nature.

Strengths/Considerations

1) By the end of 1995, the NCI intramural pediatric program had developed 28 treatment trials, of which it had initiated 27 and completed enrollment for 18. At that time, a total of 483 new patients had entered this program. Because many children have participated in more than one study, the total number of protocol participants was 664. Sixty-six new study participants were enrolled in 1995. As of January 1996, there were nine studies actively accruing patients. Dr. Pizzo has been the key investigator during this program. With the anticipated departure of Dr. Pizzo later this year, NCI should reassess the extent of its commitment to pediatric HIV clinical trials.

2) The success of this effort is reflected in the publication of 15 articles (two of which are collaborative efforts with the ACTG) in first-rank journals describing the primary results of clinical trials. Many other articles (118) describe secondary observations from the patient populations studied, case reports, laboratory investigations, editorials, and chapters in books.

3) Consistent and significant achievement that helps to define the standard of care for children has been accomplished at a cost of $1.1 million in FY 1995 (not including personnel costs).

4) To date, NCI investigators have been able to perform pharmacokinetic and Phase II trials more rapidly than the pediatric ACTG.

5) Because participants are referred to NCI for trials, this program does not have access to pregnant women or neonates who typically receive their care locally. Many of the children to whom NCI has access have advanced disease and have received previous treatment. While this may complicate assessment of toxicity, it does provide a patient resource to perform needed studies in the management of OIs and malignancies.

Opportunities

1) The NCI investigators have the opportunity to pursue novel research initiatives using the resources of the NIH Clinical Center that are not readily available to extramural investigators.

2) As mentioned earlier, the NCI effort and the pediatric ACTG should collaborate and complement the work being done by each.

Needs

1) There is redundance and competitiveness in both the capability and the scientific agendas of the NCI intramural program and the pediatric ACTG. For example, the NCI has recruited extramural sites to enroll patients in intramural studies. This is counterproductive.

2) The high cost of the NCI pediatric effort should be examined carefully. Consideration should be given to enhancing cost-effectiveness and possibly to decreasing funding.

3. NIMH and NHLBI Contributions to Pediatric Trials

NIMH and NHLBI both contribute limited funds targeted to support of specific aspects of the pediatric ACTG. NIMH has supported ACTG 188, a study that evaluates the optimal age-adjusted neuropsychologic assessment of children enrolled in trials. (See Pediatric ACTG section). NHLBI supports the production of HIVIG for an ACTG trial to decrease perinatal transmission at a cost of $3 million annually.

C. Other ICD Programs

1. NEI Extramural Clinical Trials

Scientific Priorities

In 1988, NEI funded a cooperative agreement entitled Studies in the Ocular Complications of AIDS (SOCA). This program was originally focused on both treatment and natural history aspects of HIV-associated ocular disease. However, this group has been exclusively committed to the treatment of CMV retinitis, an emphasis that will apparently continue. SOCA underwent noncompetitive renewal in 1993 and will be subject to competitive renewal in 1998.

Strengths/Considerations

1) SOCA has three components: a coordinating center and a study chair (at Johns Hopkins University), as well as a retinal photograph reading center (at the University of Wisconsin). Support of the 15 clinic sites is by subcontract from the coordinating center, with 20 percent effort allocated for the ophthalmologist, 10-20 percent effort for an internist, and 100 percent effort for a study coordinator. Sites receive $900 per subject to cover

study-related costs. All SOCA sites receive supplemental support from other sources: nine sites use ACTG resources, seven receive funds from industry, and one receives dual support. Initial annual funding was $3 million, which had increased to $4.4 million by FY 1995. All SOCA studies receive an ACTG protocol number, and participating ACTUs receive enrollment "credit" for patients accrued to SOCA/ACTG studies. Early SOCA trials were designed without formal ACTG input, although that has recently changed. To date, 573 subjects have been enrolled in 4 SOCA trials (2 completed and 2 ongoing). With NEI support totaling $28.7 million since the network's inception, an effective, albeit costly, clinical trials network dedicated to studies of CMV retinitis has been developed.

2) SOCA trials have made important contributions to the management of CMV retinitis. In particular, the retinal photograph reading center has proven to be an invaluable resource, making a major contribution to the state of the art for evaluation of retinitis progression.

3) SOCA Phase III and IV studies have effectively built upon earlier phase studies performed by the intramural NEI clinical research program and by the ACTG.

Opportunities

1) The Panel felt that ophthalmologic expertise is an important component of clinical research in advanced HIV disease of adults and children. Appropriately, CMV retinitis has been the focus of SOCA studies to date. However, the strength of this network—its ophthalmologic expertise—is also its weakness. There are several reasons for this: a) CMV is a systemic disease which affects many organs as well as the eye; b) some drugs active against CMV also are active against HIV; c) new methods of virologic monitoring have changed the state of the art for evaluating both CMV and HIV; and d) there are unanswered questions about the role of CMV in HIV pathogenesis. SOCA studies have focused almost exclusively on morphologic retinal changes in response to therapy. Thus, important opportunities have been missed in the past to understand the impact on nonretinal CMV disease, on HIV disease progression, and on the interaction of HIV and CMV. These opportunities should not be missed in the future. Open, bidirectional communication with the ACTG at both the program and investigator levels is essential for optimal design of trials in CMV retinitis, so that useful clinical data are gleaned on several levels.

2) SOCA has the opportunity to integrate its clinical trials effort with that of the NIAID-supported adult network. This would provide a multidisciplinary approach to protocol design and greater cost-effectiveness.

Needs

1) The Panel expressed concern regarding the cost of SOCA studies. The total per-capita cost to NEI for each subject enrolled in a trial of retinitis therapy is approximately $50,000. Given that SOCA receives supplemental support from both the ACTG and the pharmaceutical industry, the true cost per subject is even greater. In the FY 1995 budget, activities of the SOCA coordinating center and the study chair's office accounted for

26 percent of direct costs ($957,000). In discussions with NEI staff, it was evident that funds disbursed to SOCA sites for personnel support were not always used as intended.

2) The Panel identified the lack of a true collaborative effort between NIAID and NEI at both program and investigator levels as a major drawback, despite some recent improvements in communication. Coordination of efforts should begin with protocol design, particularly with regard to CMV and HIV virologic assessments.

3) There is competition between SOCA and the ACTG for the conduct of retinitis trials, resulting in unnecessary duplication of effort. For example, both networks have initiated similar but independent studies of an adjunctive therapy. This is another area where the proposed coordinating group for clinical trials may play an important role.

4) The Panel questioned the need for reliance on ACTG and pharmaceutical resources at SOCA sites with NEI expenditures at such a high per-capita rate. The appropriateness of the level of fiscal support for the coordinating center and the chairman's office should be addressed.

5) The Panel raised concerns that communication of study results to investigators and to the community is not uniformly prompt. The Panel urges NEI to reconsider current policies, particularly the admonition that primary outcome results be published prior to presentations at scientific meetings. The extent to which failure to disseminate research results in a timely fashion is an Institute policy or that of its grantees needs to be resolved.

2. NINDS Extramural Clinical Trials

Scientific Priorities

Neurologic complications of HIV disease are common. AIDS dementia complex (ADC) occurs in approximately 15 percent of patients, peripheral neuropathy in 15-30 percent, and OIs of the central nervous system in 25 percent. In addition, some agents used for the management of HIV infection are themselves neurotoxic. In 1993, responding to the needs expressed by neurologists performing clinical trials within the ACTG and to the community, NINDS provisionally funded the Neurologic AIDS Research Consortium (NARC) as a program project grant for 2 years under the leadership of Dr. David Clifford, then chair of the ACTG Neurology Committee. The NARC provides financial support to neurologists at 17 ACTG sites, with a total budget of $3 million in FY 1993; unencumbered funds (approximately $1.8 million) were carried over into a third year in FY 1995. The support to each participating site is contractual. Funds are primarily used to reimburse sites on a capitated basis for enrollment in studies of neurologic disease or neurology substudies of antiretroviral trials.

Strengths/Considerations

1) The strengths of the NARC mechanism include provision of direct support for the neurologists who design and conduct clinical trials. Trial development and initiation have occurred more rapidly than possible using an R01 support mechanism (on which this

Institute relies almost exclusively). As of the end of 1995, 408 subjects have been enrolled in two neurology studies, and one antiretroviral substudy focused on neurologic evaluations.

2) NARC-supported trials are cost-effective, with a per-capita cost of approximately $2,735 to date, because these trials use the existing infrastructure of the adult ACTG. NARC funds are used to support neurologists and other skilled clinicians for neuropsychologic evaluations and specialized neurologic testing.

3) NINDS and NIAID have collaborated well at both program staff and investigator levels in developing and supporting this effort. However, it is unclear whether NINDS has an interest in maintaining the supplementary support for neurologists to conduct clinical trials in HIV disease. The fact that support was limited to 2 years belies an understanding of the time frame in which clinical trials are designed, conducted, and analyzed. The Panel felt that there was little apparent commitment to either continuing this program or to supporting other means of conducting clinical trials in HIV disease.

Opportunities

1) Neurologic expertise is essential to the evaluation of antiretroviral therapy for adults and children, for the conduct of interventional studies for the neurologic manifestations of HIV infection (such as peripheral neuropathy and ADC), for the study of opportunistic diseases of the central nervous system (such as progressive multifocal leukoencephalopathy), and for the evaluation of potential neurotoxicity of investigational agents. By providing limited support for a few specified adult clinical trials, the NINDS misses the opportunity to make significant contributions to the management of the full spectrum of HIV-associated neurologic disorders in adults and children.

2) NINDS leadership expressed reluctance to commit funds to clinical trials that are not perceived as exciting or innovative and of high scientific merit as assessed by peer review. However, the Panel feels strongly that NINDS has a responsibility to patients and to its constituent academic community to provide an appropriate level of support for neurologic clinical trials. This could be accomplished in the future by supporting an infrastructure for the conduct of neurologic studies within the proposed adult network as the NARC program project does currently. However, a longer period than 2 years must be allowed to judge its productivity fairly. Pilot and proof-of-concept studies could be supported by R01 grants, as described below for NIDDK.

Needs

The Panel urges NINDS to establish a firm commitment to clinical trials for the treatment of HIV-associated neurologic disease. The current level of commitment is in sharp contrast to other ICDs and seems inappropriate, given the prevalence of neurologic disorders in HIV-infected children and adults.

3. NCRR Contribution of the General Clinical Research Centers

Scientific Priorities

The National Center for Research Resources (NCRR) General Clinical Research Centers (GCRC) program provides partial support for HIV/AIDS clinical trials by providing general infrastructure resources for the performance of extramural clinical research, including clinical trials as well as other HIV-directed research projects, such as epidemiology studies. Currently, approximately 20 percent of the total GCRC research effort is committed to AIDS-related clinical research, with a broad inter-institutional range of from 0 percent to more than 50 percent.

Strengths/Considerations

1) The overall current level of GCRC support for HIV-related research is appropriate.

2) Optimal use of local GCRC resources enhances the capacity of all ICDs to support the conduct of clinical trials.

3) GCRC budgets are relatively fixed. The distribution of AIDS and non-AIDS funds to a given GCRC reflects local investigator interest and the past performance of HIV-related research at that site. Therefore, there is no built-in incentive for a given GCRC to commit new resources to local AIDS-related research.

Opportunities

1) The GCRC program offers a unique opportunity for investigators to develop their own local therapeutics research program. GCRC support for the generation of preliminary data from local studies enhances the effort of investigators for submitting proposals for independent, investigator-initiated clinical trials research.

2) Optimal use of the GCRC mechanism increases the effectiveness of NIH funds already committed to clinical research and should be encouraged. This includes the ability to create satellite GCRC clinics. The physical separation of GCRC and AIDS clinical research sites at some universities may be a barrier to use of the GCRC by investigators reviewing NIH support for the conduct of trials on HIV diseases, because the GCRC is difficult to access by debilitated patients.

3) NCRR should view as a high priority the optimal use of the GCRC mechanism for making scientific contributions to the AIDS research mission.

Needs

1) All GCRC applications for future funding should include realistic plans for HIV-related research appropriate to that institution.

2) NCRR should disseminate information to all investigators conducting NIH-funded clinical trials regarding ways to gain or increase their access to local GCRC resources.

3) NCRR should establish a funding incentive for local GCRC programs to support HIV/AIDS clinical trials. The inter-institutional range for fiscal support of HIV/AIDS research by the GCRC program is exceedingly broad and may indicate instances where such work lacks the support of the local GCRC.

4. Office of Alternative Medicine

Scientific Priorities

The Office of Alternative Medicine (OAM) in the Office of the Director, NIH, initiated efforts in the AIDS field with the establishment of a Center on AIDS Studies at Bastyr University in Seattle, Washington, and a few small pilot grants. The Center primarily focuses on a survey of alternative medicine practices and on correlating these with medical care outcomes.

Strengths/Considerations

The Panel agreed that alternative medical approaches for the treatment of HIV infection are a valuable area of investigation. The use of such therapies is widespread among all demographic segments of the HIV-infected population and represents a significant commitment of resources both for patients and, to some extent, third-party payers. It is reasonable to investigate these alternative therapies more carefully to:

- Characterize the toxicities of these therapies;

- Determine which of the many approaches offer potential benefit; and

- Document the impact of alternative care on replacement of or on the interaction with conventional treatments of proven benefit.

Opportunities

The OAM has a major opportunity to provide the leadership required to evaluate nontraditional therapies. While AIDS/HIV infection is but one area within alternative therapeutics, it may be the one where such approaches are used to the greatest extent.

Needs

OAM staff are seeking ways to define an appropriate methodology for the evaluation of alternative therapies; for example, to determine how a controlled trial of acupuncture should be designed. The Panel was concerned that evaluation should proceed using established rigorous methods and strongly recommends attention to several principles in the implementation of the OAM program:

a) The clinical evaluation of alternative therapies should be performed in well-designed controlled studies. Only such studies will provide results that will be accepted by most investigators, practitioners, and patients, thus permitting translation into larger Phase II/III trials and into general clinical practice.

b) The evaluation of alternative therapies should include objective parameters in the assessment of response and efforts to ascertain the treatment's mechanism of action.

c) Studies should include the careful assessment of toxicity (and interactions with proven conventional treatments) as well as activity.

d) In addition to carefully defined clinical endpoints, medical outcomes assessment (quality of life, health care utilization, and cost) should be considered in the design of the evaluation of alternative therapies.

5. NIDDK Extramural Trials

Scientific Priorities

AIDS wasting syndrome (AWS) is the major focus of NIDDK-supported clinical investigation and the subject of several exploratory clinical trials. A mechanistic understanding of the pathogenesis of AWS is just emerging and will provide a basis for a rational approach to the design of therapeutic interventions. A stepwise pattern of intermittent wasting interspersed with stable weight has been identified in a majority of AWS patients. Factors contributing to AWS have been identified, including decreased caloric intake during infectious episodes, the lack of a normal adaptive response to protein-calorie malnutrition with a compensatory decrease in resting energy expenditure, the altering of lipid metabolism, a reduction of energy utilization resulting in inanition and muscle wasting, and the incidence of hypogonadism.

Strengths/Considerations

1) The NIDDK has supported small, intensive basic and applied clinical research studies in metabolic and endocrine disorders, including wasting syndrome, as investigator-initiated grants. NIDDK staff have assumed that useful therapeutic approaches and paradigms for patient assessment will be utilized subsequently by the adult ACTG for the conduct of large, randomized comparative trials. This assumption has not yet been fully tested, but it offers a potential model for inter-Institute collaboration. Strategies to identify patients at risk for AWS and to prevent or delay this complication have been developed and are under investigation. Pilot studies evaluating a range of interventions may identify subsets of patients who might benefit from particular interventions, and should provide some limited information on whether certain interventions are more effective alone or in combination. These studies will help identify agents that appear promising on the basis of changes in weight, body composition, or metabolic parameters. For example, while body composition data on growth hormone appears promising, it is not known whether growth hormone should be used chronically or episodically to avert rapid weight loss, or whether equal

benefit can be derived from less costly anabolic interventions. These questions can only be answered by large-scale comparative trials.

2) Prior to 1994, NIDDK-supported investigators had conducted pilot studies involving potential therapeutic interventions under three grants. Important observations about the potential role of recombinant human growth hormone for the treatment of AWS led to a multicenter trial that was conducted with industry support. This study demonstrated short-term weight gain, increase in lean body mass, and decrease in body fat in men.

3) In 1995, three R01 grants and two P01 subprojects have supported clinical trials to evaluate nutrient supplementation, exercise, appetite stimulants, and anabolic agents (growth hormone, testosterone), alone and in combination, as therapy for AWS. These studies have a mechanistic focus and may identify subsets of patients in which specific interventions may be effective.

4) NIDDK-supported investigators recently have begun to collaborate with NIAID-supported researchers in the adult ACTG. Several NIDDK investigators are contributing to the scientific leadership of the ACTG through the Wasting Syndrome Working Group. An initial comparative study is being developed.

Opportunities

1) Each of the multiple factors which may contribute to AWS represents a potential target for intervention. Thus potential therapies available for critical outcomes-based evaluation include nutritional supplementation, appetite stimulants, androgen replacement, growth hormone and other anabolic agents, exercise, cytokine antagonists, and metabolic inhibitors.

2) Potential advances that emerge from successful pilot and proof-of-concept studies supported by NIDDK can be evaluated subsequently in randomized comparative Phase II/III trials by the proposed NIAID-sponsored adult trials network.

3) There may be similar opportunities for broad clinical trials evaluation of the management of children with advanced HIV disease, once the essential exploratory studies have been done.

Needs

Overall, the Panel was highly impressed by the NIDDK approach to interdisciplinary, inter-Institute collaboration. The only areas that the Panel feels need attention are:

1) Communication between NIDDK and NIAID program staff should be improved so that there is an optimally smooth transition between the NIDDK-supported proof-of-concept studies and definitive clinical investigations within the current and proposed NIAID networks.

2) Currently there is no funded metabolic/endocrinologic research in pediatric HIV disease. The Panel felt that this area warrants investigation.

3) Communication and collaboration between NIDDK, NIAID, and NICHD should be supported and fostered by the proposed coordinating group.

6. NIMH Extramural Trials

Scientific Priorities

Therapeutics research represents only $3.2 million of the $87 million total NIMH budget for AIDS research. In 1994, the Institute of Medicine (IOM) reviewed the AIDS research portfolio of the Institute and recommended that NIMH work together with the NIDA and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to investigate interactions between psychotropic, antinarcotic, and antipsychotic agents and drugs used to manage HIV infection and its associated OIs.

Strengths/Considerations

NIMH has elected to use primarily Program Announcements, R01s, and interagency agreements to enhance existing clinical trials efforts, rather than create its own separate trials infrastructure. A Phase II study of peptide T, originally discovered by NIMH intramural scientists, is the glaring exception to this approach. After peptide T was rejected for further investigation by the ACTG in 1987, a joint internal NIMH-NIAID panel recommended that a limited Phase II study be conducted by NIMH. A study was designed with a sample size of 215, and a contract was awarded to a single center to perform this trial. Ultimately, two more sites were required to complete accrual into the study, and a statistical center was funded to manage and analyze the data. The study, which took over 4 years to complete at a total cost of $10 million, failed to show a treatment benefit. NIMH staff have said that they would not take the same approach to clinical investigation again, although they maintain that the neurocognitive evaluations developed for the peptide T trial may be useful in future studies.

Two joint studies are being conducted with the adult and pediatric ACTGs with ancillary support from NIMH: (1) ACTG 301, a study of treatment for ADC in adults with approximately $350,000 additional funding from NIMH to be used for neuropsychological testing, and (2) ACTG 188, a study evaluating neurodevelopmental assessment of children, described above under Pediatric Trials.

Opportunities

1) There is an opportunity for collaborative clinical research between NIMH-supported investigators and the proposed integrated adult trials network in the area of treatment of neurocognitive and psychiatric disorders.

2) There is a parallel opportunity to collaborate effectively with the pediatric ACTG on the management of neurodevelopmental abnormalities in children.

Needs

1) NIMH should not again create an independent, expensive infrastructure for the conduct of clinical trials such as the peptide T study.

2) NIMH should be represented on the current ACTG Neurology core committee and on the neurology/neuropsychological component of the proposed adult trials network.

3) Communication and collaboration between NIMH and other Institutes involved in these areas (notably NINDS, NIAID, and NICHD) should be supported and fostered by the proposed coordinating group.

7. NIDA Extramural Trials

According to NIH budget figures for FY 1994, NIDA committed $4.2 million to extramural research for the "treatment of HIV-associated complications," representing 3.1 percent of NIDA's total AIDS budget. Review of the funded projects, using the ARIS and CRISP databases, failed to reveal a single project that could be described as research on HIV/AIDS therapeutics, although some funded research project grants were studies of therapeutic intervention for drug abuse. This points out the compelling need for better definitions of AIDS and AIDS-related research and adherence to those definitions.

D. Other Considerations

1. Relationship of NIH AIDS Clinical Trials to Those of the Pharmaceutical Industry

Strengths/Considerations

There is a widespread perception that the NIAID ACTG network has had some difficulty obtaining industry collaboration. The NEI's SOCA has recently sought industrial cosponsorship. In contrast, the CPCRA network has not actively sought industry partnership. Collaboration can be mutually beneficial to the trials network, industry sponsors, and the entire AIDS clinical research enterprise. There is a longer history with the ACTG than with other programs; thus, much of the evaluation that follows is directed to this network. However, the principles enunciated apply broadly to all joint clinical trials research endeavors between industry and Government. Reluctance on the part of the pharmaceutical industry to provide investigational drugs or other support for clinical trials is multifactorial, including:

a) Concerns about the timeliness of study initiation following the development of a concept. In general, there is a perception that industry can mount a study more rapidly than would be possible working through the federally supported system, although there are no definitive data to support that contention.

b) Concerns about the availability of study data to the industrial sponsor for preparation of reports that meet internal requirements in an acceptable time frame, including access to

specific information necessary to meet corporate reporting requirements for safety and efficacy.

c) Conflicts inherent in having differing primary goals: drug development leading to product registration for the pharmaceutical company versus the broader scientific goals of the academic-based investigator community.

There are also advantages to working within the NIH-supported trials networks:

a) Ready access to a large standing cohort of investigative sites with proven ability to conduct high-quality research.

b) Reduction in costs (although the magnitude of the savings depends on the specific arrangements made).

c) A standing, independent Data and Safety Monitoring Board (DSMB) with more than 9 years of experience in this specific area and access both to unblinded trials data and to other relevant information necessary to meet its decision-making responsibilities.

d) Independent data management and statistical analysis eliminates any suggestion that the pharmaceutical sponsor has in any manner influenced the data or provided a less-than-totally-objective analysis of the results.

Opportunities

1) There is an opportunity to delineate the types of trials appropriate for direct industry sponsorship versus those more appropriate for Federal support. Theoretically, NIH-sponsored trials should not perform studies that need to be conducted for registration and for which the company has adequate capacity (internally or through contract research organizations), unless an important scientific hypothesis that the pharmaceutical sponsor would not have addressed will be tested within the study framework.

2) A full understanding or acceptance of the needs of the corporate sponsor has been variable. There is an opportunity to direct more effort at addressing industry's established concerns.

3) The ACTG has established and continues to develop a knowledge base with regard to the design of studies, particularly with respect to the use of surrogate markers, an understanding of resistance, and clinical trials methodology for studies of antiretroviral therapies and the management and prevention of opportunistic diseases. Provision of additional fiscal support from industry for ancillary laboratory studies should be encouraged, as data from such studies will enhance and extend the interpretation of trial results.

4) Opportunities should exist for companies and the clinical trials network to make alternative arrangements for key aspects of study management when the situation warrants it. For example, it should be possible, in particular circumstances, for the industrial sponsor to

assume responsibility for field-monitoring data analysis and/or data management for a specific trial.

5) Access to interim efficacy data must be restricted to the DSMB and not be provided to representatives of the pharmaceutical sponsor. For NIH-supported trials to maintain independence and scientific integrity, established interim monitoring procedures should be clearly defined and communicated to all potential pharmaceutical partners.

Needs

1) A more effective interface is needed between the pharmaceutical industry and NIH-sponsored clinical trials. The proposed independent coordinating group described earlier should develop a policy regarding the appropriate boundary between industry-sponsored and federally supported trials.

2) Studies with a major potential public health impact may be a priority to both the corporate sponsor and the NIH. In other instances, the corporate sponsor may find a study to be important but not critical to corporate priorities and, therefore, may elect to accede decision-making to the network. There is a need to set priorities for trials that will be conducted with full or partial Federal support.

3) Criteria should be developed for collaborative funding from industry for complex trials that attempt to gather critical ancillary data, specifically sophisticated laboratory analyses. The extent of such support must be incorporated into the trial planning process. When assays have become "standard of care" and are not restricted to the investigational setting, it may no longer be appropriate to assume that industry should bear the full costs of such testing. When the corporate sponsor(s) do agree to support the costs of ancillary assays, a uniform approach should be promulgated at the network operations center to ensure equitable and appropriate cost-accounting and disbursement to specified laboratories.

4) The development of a comprehensive clinical trial agreement (CTA) between the network and the industrial sponsor should be a priority. The CTA should delineate the respective roles and responsibilities for all key elements of study development and conduct, including fiscal obligations of each party.

5) More attention should be directed toward the specific needs of pharmaceutical sponsors to meet corporate requirements with respect to the collection and reporting of information (including followup data) on adverse events. Substantial barriers currently exist for timely access to critical information. A better understanding of industry standards for responsibility and accountability should be acquired by the NIH regulatory affairs staff.

6) The NIH should ensure the full and equal participation of industrial scientists in the protocol development process and in the implementation and conduct of clinical trials.

7) More effective coordination with the FDA is desirable when pivotal trials are to be conducted within the Federal clinical trials network. With most studies now involving multiple drugs and industry sponsors, redundant analyses of data are not desirable.

8) More flexibility should be encouraged to ensure that the needs of both the network and the sponsor are met. For example, to meet accrual goals within a desired time frame, additional sites, funded exclusively by the industrial sponsor, could be permitted to participate in network trials.

2. AIDS Clinical Trials Databases

The Panel recommends that a standard for databases for all NIH-funded HIV/AIDS clinical trials be developed which would facilitate cross-study and longitudinal analyses. These standards should address compatibility of database software, common variable names and definitions, and common conventions for followup. These standards must allow for sharing of data between studies within a given network and studies across networks, and should apply at least to a minimal data set of key baseline, outcome, compliance, and toxicity data. Currently, each statistical center has developed its own database, and compatibility between them is very limited. Current patient-based rather than study-based databases are advantageous in that they are much less cumbersome and, therefore, more cost-effective. For example, within the ACTG, each trial has a unique database structure, requiring time-consuming study-specific programming in order to perform key outcome analyses. In order to facilitate collaboration and cooperation among NIH AIDS clinical trials programs, all future trials networks should be subject to such standards. Where possible and as needed, existing or completed NIH AIDS trials should have their databases abstracted to the minimal data set and converted to the new standards.

There is an opportunity for specific research in clinical trials methodology itself. These areas include innovative approaches to study design, endpoint definition, surrogate marker validation, data capture and verification, statistical evaluation, and assessment of quality of life and pharmacologic-economic parameters. Currently, the few research project grants in clinical trials methodology are directed toward research on statistical approaches. Support for research project grants across a broader range of methodological issues is clearly warranted and should be encouraged by NIH program staff.

Appendix A

Biographies of Panel Members and Consultants

Richard James Whitley, M.D., a 1967 graduate of Duke University, received his M.D. degree from the George Washington University School of Medicine in 1971 and completed post graduate training at the University of Alabama at Birmingham (UAB) in 1976. Since being named Assistant Professor of Pediatrics at UAB in 1976, Dr. Whitley has taken on greater responsibilities within the Medical Center, rising through the academic ranks to become full Professor in Pediatrics, Microbiology and Medicine. In addition, he holds appointments as Scientist in the Cancer Research and Training Center, Associate Director in the Center for AIDS Research, Vice Chairman in the Department of Pediatrics, and is the 1992 recipient of the Loeb Eminent Scholar Chair in pediatrics. Dr. Whitley's numerous awards and honors include the 1991 Award for Excellence in Pediatric Research, American Academy of Pediatrics; and the 1991 Canon Ely Lecturer, Harvard School of Medicine, Children Hospital in Boston, MA. He is a member of the Society for Pediatric Research, the Infectious Diseases Society, the American Society for Microbiology, the American Society for Virology, the Pediatric Infectious Diseases Society, and the International Society for Antiviral Research. Dr. Whitley has served on numerous national and international committees, including several at the NIH. He has made significant contributions to the scientific literature, publishing more than 30 journal articles, book chapters, editorials and abstracts, and editing or co-editing several important medical books on infections and viral diseases.

Richard Ambinder, M.D., Ph.D., is the Director of the Lymphoma Program at The Johns Hopkins Oncology Center and is Associate Professor of Oncology and Pharmacology. Dr. Ambinder received his B.A. from Harvard College in 1975. The remainder of his training has been at Johns Hopkins University where he received his M.D. in 1979, trained in Internal Medicine and Oncology, and earned a Ph.D. in Pharmacology in 1989. He is board certified in Internal Medicine and Oncology. He is a Leukemia Society Scholar and co-chairs the Eastern Cooperative Oncology Group AIDS Committee and is Laboratory Chair of the AIDS Oncology Consortium. He has authored over 80 scientific publications. Dr. Ambinder's areas of expertise include Epstein-Barr virus molecular biology, the treatment of hematologic malignancies, treatment of AIDS associated malignancies, and bone marrow transplantation. His studies attempt to define the role(s) of Epstein-Barr virus in the pathogenesis of tumors in order to the develop strategies to diagnose and treat those malignancies, specifically, a way to utilize the presence of the virus or viral gene expression to improve diagnosis or to target therapy.

Deborah Cotton, M.D., M.P.H., is Associate Professor of Medicine, Harvard Medical School, and Associate Professor in the Department of Health Policy and Management, Harvard School of Public Health. She is an investigator at both the Massachusetts General Hospital AIDS Research Center and the Center for Biostatistics in AIDS Research (CBAR) at the Harvard School of Public Health. Dr. Cotton received her M.D. degree from Boston University in 1976 and an M.P.H. in epidemiology from Johns Hopkins University in 1985. She completed her internship and residency at Beth Israel Hospital in Boston, and was a Clinical Associate in the Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Disease, and a

Senior Staff Fellow in the Clinical Oncology Branch, National Cancer Institute. She is board certified in internal medicine and infectious diseases. Dr. Cotton's research concerns the clinical epidemiology of HIV infection. She is the author or co-author of over 50 scientific publications and book chapters and is co-editor of a book on AIDS in women which will be published later this year. Dr. Cotton formerly chaired the Antiviral Advisory Committee of the Food and Drug Administration and served on the Clinton Administration's National Task Force on AIDS Drug Development. She is a member of the Board on Health Sciences Policy at the Institute of Medicine.

Janet H. Darbyshire, M.B.C.hB, received her medical degree from the University of Manchester in 1970, and M.Sc. in Epidemiology from the London School of Hygiene and Tropical Medicine in 1989. She became a member of the Royal College of Physicians in the United Kingdom in 1973 and was elected a Fellow in 1988. After clinical training in Medicine she joined the Medical Research Council (MRC) Tuberculosis and Chest Diseases Unit in 1974, and was responsible for coordinating controlled clinical trials and epidemiological studies in tuberculosis and respiratory disease in the United Kingdom and East Africa. Following the closure of the Unit in 1986, she became Head of the MRC Cardiothoracic Epidemiology Group where she continued the program of work in tuberculosis and respiratory diseases. In 1989, she became responsible for the MRC HIV Clinical Trials Centre which coordinates the MRC's program of clinical trials in HIV infection in the UK, in collaboration with other European countries and Australia. Her research interests primarily focus on multicenter, multinational clinical trials and related epidemiological studies in tuberculosis and respiratory diseases and, more recently, on HIV infection.

Lynda Dee, Esq., is a practicing attorney licensed in Maryland. Ms. Dee has been involved in AIDS issues since her husband was diagnosed with the disease in 1986. She was a founding member of, and has served as President of AIDS Action Baltimore since 1987. She is a participant in the Community Constituency Group and the Opportunistic Infection and Executive Committees of the AIDS Clinical Trials Group.

David L. DeMets, Ph.D., is presently Chair, Department of Biostatistics and Professor of Statistics and Biostatistics at the University of Wisconsin. He received his B.A. from Gustavus Adolphus College in Mathematics in 1966 and an M.S. and Ph.D. in Biostatistics from the University of Minnesota in Biostatistics in 1968 and 1970. Dr. DeMets' research interests include methods for design and analyses of epidemiologic studies and clinical trials, sequential methods used for interim analyses, monitoring data from clinical trials, survival and longitudinal studies, and collaborative work in cardiovascular diseases, cancer, ophthalmology, diabetes and AIDS.

Wafaa El-Sadr, M.D., M.P.H., is the Director of the Division of Infectious Diseases at Harlem Hospital in New York City and Associate Professor of Clinical Medicine at Columbia College of Physicians and Surgeons. Dr. El-Sadr received her M.D. degree from Cairo University, Egypt, and M.P.H. degree from Columbia University. She trained in internal medicine at Cabrini Hospital/New York Medical College, and in infectious diseases at VA Medical Center/New York University and Case Western Reserve University. She is board certified in both Internal Medicine and Infectious Diseases and is active in clinical care and research issues

related to HIV and TB. She is the principal investigator for the Harlem AIDS Treatment Group, one of the NIAID-funded Community Programs for Clinical Research on AIDS. She is a member of various advisory committees. Her research interests include design of HIV-related clinical trials, opportunistic infections in HIV, complications of HIV infection in women, HIV-related tuberculosis, and participation of minorities and women in clinical trials.

Christina M. Marra, M.D., is Assistant Professor of Neurology and Medicine (Infectious Diseases), University of Washington, Seattle. Dr. Marra received her M.D. from the Oregon Health Sciences University in 1984 and completed a residency in neurology in 1988 and a fellowship in infectious diseases in 1992 at the University of Washington. She is board certified in Neurology and is author of 35 scientific publications, including 15 book chapters. Dr. Marra's areas of expertise include neurologic manifestations of HIV and other infectious diseases.

John Martin, Ph.D., is Chief Operating Officer for Gilead Sciences, a Foster City, CA company specializing in the development of antiviral agents. Prior to joining Gilead, he was employed by Bristol-Myers Squibb and Syntex, where he was the co-inventor of ganciclovir. His research has focused on the synthesis and evaluation of antiviral nucleoside and nucleotide analogues. He received a Ph.D. degree in organic chemistry in 1978 from the University of Chicago.

Julio S.G. Montaner, M.D., FRCPC, FCCP, was born in Buenos Aires, Argentina, where he received his M.D. with honors at the University of Buenos Aires. In 1988, Dr. Montaner joined the Faculty at St. Paul's Hospital, University of British Columbia as the Director of the AIDS Research Program and the Infectious Disease Clinic. Dr. Montaner has been a National Health Research Scholar of Health Canada since 1988. He is the Director, Clinical Activities of the BC Centre for Excellence in HIV/AIDS and a founding co-Director of the Canadian HIV Trials Network. He is an Associate Professor in the Department of Medicine at the University of British Columbia. In 1996, Dr. Montaner was appointed to the Endowed Chair on AIDS at St. Paul's Hospital, University of British Columbia, the first such initiative in Canada. He has published extensively with regard to antiretroviral therapies and respiratory complications of HIV. Most importantly, he pioneered the use of corticosteroids as adjunctive therapy for AIDS-related *Pneumocystis carinii* pneumonia for which he received the Young Investigators Award of the American College of Chest Physicians in 1989. Recently Dr. Montaner was awarded the 1995 Pasteur Prize (Canada) for his contributions to Clinical Research in the field of HIV/AIDS. He is a member of the Scientific Committee for the Retroviral Conference of the IDSA; the International Conference on HIV Therapy; and the Steering Committee on Vaccine Development for the WHO Global Program on AIDS. He co-chairs the Scientific Program and is a member of the Organizing Committee for the XIth International Conference on AIDS. He serves on review committees for the NHRDP/MRC in Canada, the NIH in the United States, PAHO, and WHO, among others. He is also an active reviewer for a number of peer-reviewed journals.

Maureen W. Myers, Ph.D., is the Clinical Program Director for Virology at Boehringer Ingelheim Pharmaceuticals, Inc., in Ridgefield, CT. Dr. Myers received her doctorate in Microbiology from Georgetown University School of Medicine and Dentistry in 1975. She

served as staff fellow/senior staff fellow in the Laboratory of Experimental Pathology of the NIAMS, NIH, from 1975-1979. Her research focussed on the effect of interferon on MuLV replication and later, in conjunction with Dr. Barrie Carter, the replication of adeno-associated virus. In 1979, she was selected for the NIH Grants Associates Program. Upon completion of this intensive, 1-year training program in science administration, Dr. Myers was appointed as the Antiviral Substances Program Officer in the Microbiology and Infectious Diseases Program of the NIAID, a position responsible for both preclinical and clinical evaluation of antiviral agents. In 1985, she was invited by Dr. Anthony Fauci, Director, NIAID, to establish what was to become the Treatment Research Branch of the AIDS Program. Dr. Myers was the driving force behind the establishment of the AIDS Clinical Trials Group and remained responsible for this effort through the end of 1990. In 1991, she joined Boehringer Ingelheim Pharmaceuticals as a Senior Associate Director responsible for the clinical development of the nonnucleoside reverse transcriptase inhibitor, nevirapine. She is the recipient of a number of awards and honors, including the NIH Director's Award in 1985 and the Public Health Service Special Recognition Award in 1988. Her scientific interests include antiviral drug development, HIV therapeutics, interim monitoring of trials by Data Safety and Monitoring Boards, and clinical trial conduct and methodology.

Roger J. Pomerantz, M.D., is Professor of Medicine at Thomas Jefferson University and Chief of Infectious Diseases and Director of the interdepartmental Center for Human Retrovirology at the University. Dr. Pomerantz received his M.D. from Johns Hopkins University School of Medicine in 1979 and completed a Medical Internship and a Junior plus Senior Residency in Medicine at Massachusetts General Hospital of the Harvard Medical School in Boston. He completed an Infectious Disease Fellowship at Massachusetts General Hospital and was a postdoctoral fellow in its laboratory of retrovirology and also the Chief Medical Resident. He served as visiting scientist at the Whitehead Institute at the Massachusetts Institute of Technology between 1988 and 1990. Dr. Pomerantz's laboratory interests include HIV-1 molecular pathogenesis, neuropathogenesis, molecular transmission, genetic therapy of human retroviral diseases.

William G. Powderly, M.D., is Associate Professor of Medicine and Co-Director of the Division of Infectious Diseases at Washington University School of Medicine, St. Louis, MO. Dr. Powderly received his M.B., B.Ch., B.A.O. from University College Dublin, Ireland, in 1979 and subsequently his M.D. from the same institution in 1987. He completed residency in Internal Medicine at St. Vincent's Hospital in Dublin and a fellowship in Infectious Diseases at Washington University, where he has been the director of the AIDS clinical trials unit since 1987. Dr. Powderly was elected a Fellow in the Royal College of Physicians in Ireland in 1992. His research focuses on medical mycology and infections such as AIDS in immunocompromised hosts, with particular emphasis on clinical trials of new antiretroviral agents and of therapies of opportunistic infection. Dr. Powderly has authored or co-authored over 120 scientific publications. His areas of expertise include AIDS clinical trials and opportunistic infections treatment and prophylaxis.

Peter Reiss, M.D., Ph.D., is Assistant Professor of Medicine at the Academic Medical Center, University of Amsterdam, the Netherlands. He also serves as Deputy Director of the Dutch National AIDS Therapy Evaluation Center (NATEC), which is supported by the Dutch

government to coordinate HIV/AIDS clinical trials in the Netherlands. Dr. Reiss received his M.D. from the University of Amsterdam in 1981. His medical training included electives at Harvard University (Peter Bent Brigham and Children's Hospital in Boston). He is board certified in Internal Medicine, with a subspecialty in Infectious Diseases. He has authored or co-authored over 50 publications in the field of general infectious diseases and HIV. He is an active member of the steering committees for a number of international antiretroviral clinical trials and serves on the data safety monitoring boards of such trials. He also serves as a member on the panel that annually reviews the grant proposals for the French National AIDS Research Agency (ANRS). His current research interest concerns the interaction between opportunistic infections and HIV replication as well as the effect of antiretroviral therapy on certain opportunistic infections.

Douglas D. Richman, M.D., is a Professor of Pathology and Medicine at the University of California at San Diego; Chief, Virology Section, Laboratory Service, San Diego Veterans Affairs Hospital; and Director, Research Center for AIDS and HIV Infection. Dr. Richman received his A.B. at Dartmouth College and his M.D. at Stanford University, where he completed his residency. He was a Research Associate in the Laboratory of Infectious Diseases at the National Institute of Allergy and Infectious Diseases, NIH, and a Clinical Fellow in the Division of Infectious Diseases, Beth Israel Hospital and Children's Hospital Medical Center in Boston. He is board certified in Internal Medicine and Infectious Diseases. Dr. Richman accepted a John Simon Guggenheim Fellowship and a Visiting Fellowship, Clare Hall, at the University of Cambridge in 1984-85. He received the Howard Temin Award for Clinical Sciences for Scientific Excellence in the Fight Against HIV/AIDS in 1993. Dr. Richman was awarded an NIH MERIT Award in 1994 and has been a member of the Advisory Board, International AIDS Society since 1991. He has chaired the Steering Committee on Research and Drug Development, Global Programme on AIDS, World Health Organization.
Dr. Richman's research interests have focused on several aspects of HIV infection: including the investigation of antiviral drugs and drug resistance; the interaction of HIV with different cells of the immune system (lymphocytes, macrophages); the function of the viral *nef* gene and its product; and the mechanism of lymphocyte cell killing by apoptosis. He has authored or co-authored over 290 scientific publications and 260 abstracts. He is also a Co-Editor of *Clinical Virology*, a forthcoming state-of-the-art clinical reference book, and editor of *Antiviral Drug Resistance* which is scheduled for publication in 1996.

Didier Trono, M.D., received his M.D. in 1981 from the University of Geneva, Switzerland. He completed his medical training in pathology and internal medicine and then specialized in clinical infectious diseases at Massachusetts General Hospital. From 1986-90, he was a research associate with Dr. David Baltimore, at the Whitehead Institute for Biomedical Research in Cambridge, MA. In 1990, he started the Infectious Disease Laboratory at the Salk Institute. In 1992, Dr. Trono was the recipient of the PEW Scholar for Biomedical Sciences Award. He is currently an Associate Professor at the Salk Institute.

Mark A. Wainberg, Ph.D., is director of the AIDS Centre and Professor of Medicine and of Microbiology at McGill University in Montreal, Canada. Dr. Wainberg obtained his Ph.D. from Columbia University in 1972. He was subsequently a postdoctoral fellow at the Hebrew University-Hadassah Medical School in Jerusalem, prior to obtaining an independent position at

McGill. Between 1980-1981, Dr. Wainberg completed a sabbatical year in the laboratory of Dr. Robert C. Gallo, National Cancer Institute, NIH. He was the first scientist in Canada to work on HIV and has published actively in the field, mostly in areas of HIV reverse transcriptase and HIV drug resistance. The antiviral drug 3TC was first identified in Dr. Wainberg's laboratory. Dr. Wainberg has authored or co-authored over 250 scientific publications and has contributed numerous book chapters, reviews, and other work. He is currently President of the Canadian Association for HIV Research and is the Canadian representative on the governing council of the International AIDS Society. Dr. Wainberg has helped to organize many meetings in the field of HIV/AIDS. He was the first Canadian to have been designated a national AIDS scientist by the Canadian Ministry of Health.

Catherine Wilfert, M.D., is principal investigator of the Duke Pediatric AIDS Clinical Trial Unit and Professor of Pediatrics and Microbiology at Duke University Medical Center, Durham, NC. Dr. Wilfert received her M.D. from Harvard in 1962 and did one year of residency in Internal Medicine on the Harvard Service at Boston City Hospital. She did her pediatric residency at Bowman Gray and Children's Hospital Medical Center, Boston, and completed a fellowship in Infectious Diseases at that institution in 1967. She is board certified in Pediatrics and served as Chief of Pediatric Infectious Disease from 1980 to 1993. She served as the first chair of the Pediatric ACTG and as a member and Chair of the Advisory Committee on Immunization Practices for the U.S. Public Health Service. Dr. Wilfert is Secretary-Treasurer of the Infectious Disease Society of America. Her research has focused sequentially on immunizations, enterovirus infections, and HIV infection of children. She has been an editor and author of *Zinssers Textbook of Microbiology, Infectious Diseases of Children, and Pediatric AIDS*.

Brian Wong, M.D., is Chief of Infectious Diseases at the VA Connecticut Health System and Associate Professor of Internal Medicine at Yale University School of Medicine. Dr. Wong received his M.D. degree from SUNY Downstate Medical Center in 1974. His internship, residency and chief residency were in the Department of Medicine at SUNY Downstate and Kings County Hospital in Brooklyn, NY, and he received a fellowship in infectious diseases at Memorial Sloan-Kettering Cancer Center in New York. Dr. Wong is board certified in Internal Medicine and Infectious Diseases. He has served on the faculties of Cornell University Medical College from 1980 to 84, the University of Cincinnati College of Medicine from 1984 to 1995, and the Yale University School of Medicine from 1995-present. Dr. Wong's area of expertise is infections in compromised hosts, especially those caused by medically important fungi. He has authored or co-authored over 40 scientific papers and chapters in this area.

Appendix B

Meetings Schedule[*]

May 3, 1995

August 10-11, 1995

September 18, 1995

September 28-29, 1995

October 10-11, 1995

November 13-14, 1995 (included Open Public Session)

[*]All sessions were full Panel meetings.

Appendix C

Subpanel Structure and Membership

1. NIAID Adult Trials Programs

   J. Martin (lead)
   W. Bahlman
   S. Cox
   D. Cotton
   J. Darbyshire
   D. DeMets
   W. El Sadr
   J. Montaner
   P. Reiss
   B. Wong

2. NEI and NINDS Programs

   Subpanel 1 plus C. Marra (lead)

3. Pediatric Trials Programs (NIAID, NICHD, NCI, others)

   C. Wilfert (lead)
   A. Ammann
   D. Averitt-Doherty
   E. Connor
   R. Pomerantz
   W. Powderly
   M. Wainberg

4. NCRR

   Subpanel 3 with W. Powderly (lead)

5. Intramural Adult Programs (NCI, NIAID/Clinical Center, Extramural NCI

   D. Richman (lead)
   R. Ambinder
   L. Dee
   M. Myers
   D. Trono

6. All Other ICDs

Subpanel 5; M. Myers (lead)

Appendix D

Budget Commitments by Institute for Clinical Trials, FY 1994[1]

ICD	Extramural[2]	Intramural[2]	Total	Percent[3]
NIDR	$954 (OI)	----	$954	7.99
NIDDK	700 (code 3.5) 876 (code 3.8)	---- ----	700 876	6.71 8.39
NINDS	807 (OI) 1,044 (code 3.7)	1,322 (OI) ----	2,129 1,044	9.64 4.73
NIAID	41,376 (HIV) 13,774 (immunoTX)[4] 76,613 (OI) 21,131 (3.5-3.8)	9,738 (HIV) ---- 5,433 (OI) ----	51,114 13,774 82,046 21,131	9.99 2.69 16.04 4.12
NICHD	23,203	----	23,203	43.79
NEI	4,989 (OI)	1,309 (OI)	6,298	76.88
NIMH	4,123 (HIV) 872 (code 3.7)	---- ----	4,123 872	4.99 1.05
NIDA	4,237 (code 3.8)	----	4,237	3.08
NINR	330 (immunoTX) 813 (code 3.8)	151 ----	481 813	11.67 19.73
NCRR	10,376 (HIV) 125 (immunoTX) 7,279 (OI) 4,379 (3.6-3.8)	---- ---- ---- ----	10,376 125 7,279 4,379	17.32 0.21 12.15 7.31

[1] Dollars in thousands; FY 1994 budget according to *FY 1996 Plan and Budget Estimate for Scientific Opportunities in HIV-Related Research (FY 1996 Strategic Plan)* prepared by the NIH Office of AIDS Research.

[2] The Therapeutics section of the Scientific Opportunities and Priorities in the FY 1996 Strategic Plan lists code 3.2 for "conduct clinical trials' [for HIV], distinct from the code for antiretroviral drug development. Code 3.4, "prevent and treat OIs." and analogous codes for other complications of HIV disease (codes 3.6-3.8), include both drug discovery and clinical trials, so that the proportion allotted to clinical trials alone cannot be readily determined from overall NIH budget figures.

[3] Percent of ICD's total, not percent of NIH total.

[4] ImmunoTX - immunotherapies.

Appendix E

Glossary of Terms

Status of Studies

Developed. The concept for a trial was sufficiently developed so that a protocol number was assigned and at least a draft protocol was written, but the study was never opened to enrollment.

Initiated. Patients were enrolled into the study.

Accrual completed. All required patients were enrolled; these participants may now be in the followup phase of the study.

All followup completed. All data collection has been completed although final data verification and analysis may be ongoing.

Classification of Journals

First-rank journals include the following journals: *Annals of Internal Medicine, Journal of Infectious Diseases, Journal of the American Medical Association, Journal of Pediatrics, Lancet, Nature, Pediatrics, Science,* and the *New England Journal of Medicine*.

Peer-reviewed AIDS-specific journals include *AIDS,* the *Journal of AIDS,* and others.

Peer-reviewed subspecialty journals include *Blood, Journal of Clinical Oncology*, *Neurology*, *Ophthalmology*, and numerous other journals.

Appendix F

Lost to Followup (LTFU) and Voluntary Discontinuation Rates of Representative Studies NIAID Extramural Adult and Pediatric Programs

Table 1. Adult ACTG

Study Number	Patient Population Characteristics	Number of Patients	Accrual Period (range)	Median/Mean Followup (yrs)	Voluntary Discontinuation Rate[1]	Lost to Followup Rate[2]
016	CD4>200, symp	711	7/87-7/89	.9	25.1	5.8
019a	CD4<500, asymp	1,338	7/87-7/89	1.1	18.7	6.1
019b	CD4>500, asymp	1,637	7/87-7/89	4.9	11.8	7.6
116b/17	CD4<300	913	10/89-4/91	1.1	32.7	5.0
116a	CD4<300	617	10/89-4/91	1.6	14.6	5.6
155	CD4<300	1,001	12/90-8/91	1.5	25.2	4.3
175	CD4:200-500	2,495	12/91-10/92	2.8	19.0	6.9
021	prior PCP	310	7/88-11/90	1.4	?	6.9
196	CD4<100, noMAC	1,216	4/93-2/94	1.6	14.7	4.5
204	CD4<100, noCMV	1,227	12/92-10/94	1.1	25.8	5.9

[1] The rate of voluntary discontinuation of study therapy, is computed as the number of subjects who voluntarily discontinued per 100 person-years of observation.

[2] The lost to followup rate, computed as the number of patients lost to followup per 100 person-years of observation. Followup refers to followup for **primary** endpoint only. For the antiretroviral studies, (protocols 016-175) this is typically followup for the first AIDS-defining illness or death, whichever occurs first; the LTFU rates for survival are lower much (data not shown). For OI prophylaxis studies (protocols 021-204) the primary endpoint is the OI of interest (*Pneumocystis* pneumonia, disseminated *M. avium* complex, or CMV end-organ disease, respectively). Once again, the LTFU for survival are much lower.

Table 2. Pediatric ACTG

Study Number	1º Endpoint	Number of Patients	Voluntary Discontinuation Rate[1]	Lost to Followup Rate[2]
076	Perinatal transmission, mothers, CD4+ >200	513	4.3	13.8
076	Perinatal transmission, babies	525	1.8	4.0
128	Neuropsychiatric scores	426	4.7	3.5
152	HIV progression in untreated children[3]	839	5.4	2.9

[1] The rate of voluntary discontinuation of protocol therapy is computed as the number of subjects who voluntarily discontinued per 100 person-years of observation.

[2] The lost to followup rate (LTFU), computed as the number of patients lost to followup per 100 person-years of observation. Followup refers to followup for **primary** endpoint only. For the antiretroviral treatment studies this is typically followup for the first AIDS-defining illness or death, whichever occurs first; the LTFUs for survival are much lower (data not shown).

[3] HIV progression in ACTG 152 was a complicated definition that included several factors, largely focused on the occurrence of neurodevelopmental delay and growth delay attributed to HIV infection.

Table 3. CPCRA

Study Number	1° Endpoint	Number of Patients	LTFU: 1° Endpoint[1]	LTFU: Survival
001A	Toxo. encephalitis	84	0.0	0.0
001B	Toxo. encephalitis	396	3.2	1.6
002	AIDS/death	467	7.1	0.8
007	AIDS/death	1,113	1.7	1.2
010	Candidiasis in women	323	4.0	2.4
013	PCP	72	4.6	1.3
023	CMV disease	994	3.0	1.8

[1] The rates of patients lost to followup, given separately for the primary endpoint and for survival for completed studies with time-to-event endpoints. The LTFU is expressed as the rate per 100 person-years of observation. (Voluntary discontinuation rates were not provided.)